

Does Human Papillomavirus Have Any Association with Human Colorectal Cancer? A Brief and Critical Review of the Existing Literature

Abstract

Background: The role of human papillomavirus (HPV) has already been well-studied in colorectal cancer (CRC) with conflicting results. We performed a comprehensive review of the results and methodologies used in different previous studies that associated HPV with CRC, and evaluated that how well these studies fulfill the proposed criteria for proving HPV etiology in CRC. **Methodology:** The PubMed search engine was used to retrieve all the research articles published before March 2020 to detect HPV in CRC. **Results:** In total, 40 relevant original articles were found on PubMed. Some of them were case-control studies that compared the cancerous tissue samples with the normal or benign and some were not. The positivity ratios of HPV detection was varied population-wise. In some populations, it was greater in cancerous tissue samples as compared to the normal or benign tissues, whereas in other cases, the opposite situation was also observed. A 0% HPV detection positivity ratio in cancerous as well normal or benign samples was also observed in a few cases. However, the odds ratios and confidence intervals were not reported. **Conclusion:** The results of the present study are controversial. They failed to prove the potential participation of HPV in CRC but rather suggested it as cause-effective or at least a coparticipant in the pathogenesis of CRC.

Keywords: Colorectal cancer, human papillomavirus, pathogenesis, PubMed

Introduction

Human papillomavirus (HPV) is a small double-stranded DNA virus that belongs to the Papillomaviridae family, a group of viruses that play a well-recognized etiological role in vaginal and cervical cancer.^[1-3] Until now, there are >180 different known subtypes of HPV exist in the medical literature. Out of which 15 HPV subtypes including (HPV 16, 18, 35, 31, 39, 51, 45, 56, 52, 66, 59, 69, 68, 82, and 73) are well-known key players in the pathogenesis of genital cancer, while few other HPV subtypes, including (HPV 6, 11, 43, 42, 40, 44, 61, 54, 72, 70, and 81) are considered as the causative agent of the warts of genitals and skin in both gender (male and female), mainly in females.^[4-6] Furthermore, studies have suggested the etiological role of HPV in different other malignancies such as anal, oropharyngeal, penile, vulvar, and HPV-related tumors, which together constitute 0.7% of all the carcinomas in both genders.^[7] The role of HPV

in the pathogenesis of gastrointestinal cancer is well recognized.^[8] The HPV could also infect the colon and rectum area.^[9] According to few studies, hematogenous genital sites are the major HPV-related infection sites; however, it can also spread to the distinct body parts through lymphatic ducts by creating a suitable environment for the development of colorectal cancer (CRC).^[9-11]

Global statistics declared CRC is one of the more common subtypes of cancer that contributes to most cancer-related deaths. Based on facts and figures, there are approximately 1,360,602 new cases of CRC, and 693 881 CRC related deaths are recorded every year worldwide.^[12]

Changes in the bowel movement, weight loss, stomach pain, and anemia are the most common symptoms of CRC.^[13] Mostly, CRC develops at a slow and gradual pace.^[14] It is estimated that around 50% of the sexually active people will come in contact with HPV at some point in their lives.^[13,15] In Brazilians, the prevalence of CRC varies between 35% to 72% in both genders (male and female). It was observed

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that HPV strains 16 and 18 were responsible for 55% of the total CRC cases when the precancerous lesions and lesions linked to CRC were screened in South America and the Brazilian population.^[16] Genetic predisposition, such as family adenomatous polyposis or first-degree relatives who have CRC is another risk factor for the CRC.^[17]

The understandings of CRC have become clearer at the molecular level; however, the etiology of CRC is still controversial. In the last decade, several studies have suggested the potential role of HPV in the development of CRC.^[18,19] However, the presence of HPV in colon cancer tissue remains a highly debatable topic because of the inconsistencies in result reproducibility. Since the integration of the HPV viral genome with the host genome is necessary for its carcinogenic activity, assessment of the physical status of the viral genome after the confirmation of HPV infection is essential to establish a causal association. The inactivation of the E2 gene through genomic integration enhances the expression of E6 and E7 oncoproteins, which acts as an antagonist of the tumor protein 53 (TP53) and retinoblastoma protein (pRB) and suppress their antiproliferative functions to promote the CRC development.^[20-23]

The first-ever study carried out in 1988 by Boguszaková *et al.* had shown no correlation between HPV infection and CRC. They screened the presence of HPV in a total of 10 colon cancer samples through southern blot hybridization analysis, which revealed no HPV antigen in colon cancer tissues.^[24]

After 1990, many researchers used the polymerase chain reaction (PCR) and different other techniques, including immunohistochemistry and *in situ* hybridization, to detect the HPV presence in CRC tissue specimens, but still, the outcomes are controversial. In this review article, we aimed to provide a comprehensive review of published articles which associated HPV infections with CRC, evaluation of the strengths, weakness, and the consistency of their results with Bradford hill postulates of causation (which provide epidemiologic evidence of a causal relationship between a presumed cause and an observed effect) will also remain the major focus of this review article.

Methodology

The methodology of the present study has been divided into two phases.

Literature search

All the relevant articles associating HPV with CRC were identified through an extensive and comprehensive search of the PubMed database using the keywords: “Colorectal cancer” AND “Human Papillomavirus”. We also defined the “papillomaviridae” AND “Colorectal neoplasia” terms as medical subject headings (MeSH). The Mesh terms and entry words were combined during the completion of the

search process. In total, 1363 original articles were found on PubMed before March 2020, with the “Original Article” filter.

Relevant data extraction

Out of total of 1363 original articles, the relevant articles with desired information were extracted initially by reading the title, abstract, and then the complete article.

Results

In total, 40 original articles [Table 1] were found in 16 different populations on PubMed associating HPV with human CRC. Table 1 summarizes the major information obtained from these articles, including details of the understudied population, techniques used for HPV detection, the name of the target gene, number (No.) of the screened samples (normal, benign, and cancerous) with their respective population-specific HPV detection positivity ratios. PCR technique was initially employed by most of the studies to detect the presence of HPV in cancerous and normal or benign tissue samples with the help of L1, E6 and E7 gene-specific primers specific for (6, 11, 16, 18, 31, 33, 35, 39, 40, 42, 45, and 51–59) subtypes of HPV.^[12,18,19,25-58] However. Few studies also utilized various other techniques including for HPV detection, including SPF10 INNO-LiPA,^[39] bead-based multiplex Luminex assay,^[40] Reverse southern blot hybridization,^[12,42] southern blot hybridization,^[24,45,51,54,58] pyrosequencing,^[12] Immunohistochemistry (IHC),^[50,52] and Low Ionic Strength-Single Strand Conformational Polymorphism (LIS-SSCP).^[57] Out of the total 40 studies, $n = 21$ were the case–control studies in which both cancerous and normal or benign tissues sample were screened.^[12,18,19,25,27,30,34,36,37,39,40,43-47,49,51,54,55,59]

The positivity ratios of HPV detection in CRC tissues were varied from 0%^[24,25,28,33,34,38,39,55] to 100%.^[36,58] Similarly, the positivity ratios of HPV detection in normal and benign colorectal tissues sample also varied from 0%^[12,18,25,30,40,46] to 84%^[51] and 0%^[28,34,39,40,49,55] to 69.56%^[36] respectively.

Further details regarding population-specific HPV etiology in CRC has been discussed as follow:

Until now, a single study^[24] has been performed in Czechoslovakian to identify the association between HPV and CRC through the application of southern blot hybridization. None of the 10 samples tested for HPV detection were found positive [Table 1].

In Iran, a total of 07 studies,^[25-31] including three^[25,27,30] case–control studies, have been conducted so far to establish the association between HPV and CRC. All these studies applied the PCR technique for HPV identification with the help of E6, E7, and L1 gene-specific primers. The HPV detection positivity ratios reported in these studies were varied from 0%^[25,30] to 1.25%^[27] and 0%^[25,28] to 31.5%^[60] in normal/benign and cancerous tissue samples,

Table 1: Summary of the detected human papillomavirus types and positivity rate in normal and colorectal cancer samples relative to the different selected articles

Studied population	Name of the technique used for the viral genome detection	Name of the target gene	Number of the normal samples screened	Percentage positivity of HPV in normal samples (%)	Number of the adjacent or benign samples screened	Percentage positivity of HPV in adjacent or benign samples (%)	Number of the total CRC samples screened	Percentage positivity of HPV in CRC samples (%)	References
Czechoslovakia	Southern blot hybridization	-	-	-	-	-	10	0	[24]
Iran	PCR	L1	50	0	0	0	50	0	[25]
	PCR	L1	0	0	0	0	100	1	[26]
	Nested PCR	L1	80	1.25	0	0	80	6.25	[27]
	PCR	L1	0	0	60	0	70	0	[28]
	Nested PCR, real time PCR	E6, E7	0	0	0	0	38	31.5	[29]
	PCR	E6	70	0	70	5.7	70	2.85	[30]
	Qualitative real time PCR	L1	0	0	0	0	84	22.6	[31]
Poland	-	-	-	28	-	56	-	67	[32]
	PCR	E6, E7	0	0	0	0	186	0	[33]
	Real time PCR	L1	0	0	10	0	40	0	[34]
	PCR	-	0	0	0	0	50	20	[35]
	Real time PCR	-	0	0	23	69.56	1	100	[36]
Hispania	Nested PCR	L1	36	2.8	0	0	45	42.2	[37]
US	PCR	L1	0	0	0	0	50	0	[38]
	Nested PCR and <i>in situ</i> PCR	L1, E6	10	0	0	0	55	51	[18]
	PCR, SPF10 INNO-LiPA method	L1	0	0	30	0	73	0	[39]
	Real-time PCR, bead-based multiplex Luminex assay	E6, E7	250	0	254	0	0	0	[40]
Italy	Real-time PCR.	L1, E7	0	0	0	0	555	2	[41]
	PCR, Reverse blot hybridization	L1, E6, E7	0	0	0	0	66	33.3	[42]
India	Degenerate PCR	L1	0	0	57	8.8	57	15.8	[43]
	PCR	L1	0	0	30	20	93	36.5	[44]
China	PCR, Southern blot hybridisation.	E6, E7	0	0	37	29.7	70	52.9	[45]
	PCR	-	16	0	10	10	46	43.47	[46]
	PCR	L1	0	0	32	3.1	32	21.9	[47]
	PCR	E7	0	0	82	4.87	82	51.21	[48]
	PCR, Reverse Southern blot and pyrosequencing	L1	32	0	0	0	96	33.3	[12]
	PCR	L1	0	0	75	0	75	73	[49]
	Multiplex PCR, IHC	L1, E6	0	0	0	0	232	14.2	[50]
Brazil	Nested PCR	L1, E6, E7	72	19.4	72	50	72	63.9	[19]
Taiwan	PCR, Southern blotting	-	19	84	0	0	19	53	[51]
	Nested PCR, IHC	L1, E6	0	0	0	0	69	16	[52]
Israel	PCR, SPF10 INNO-LiPA method	L1	0	0	30	0	106	0	[39]
	PCR, SPF10 INNO-LiPA method	L1	0	0	30	0	100	0	[39]

Contd...

Table 1: Contd...

Studied population	Name of the technique used for the viral genome detection	Name of the target gene	Number of the normal samples screened	Percentage positivity of HPV in normal samples (%)	Number of the adjacent or benign samples screened	Percentage positivity of HPV in adjacent or benign samples (%)	Number of the total CRC samples screened	Percentage positivity of HPV in CRC samples (%)	References
Turkey	PCR	L1	0	0	0	0	53	81.2	[53]
	PCR, southern blot hybridization	-	0	0	56	32	56	82.14	[54]
	PCR	L1	0	0	49	0	106	0	[55]
Argentina	Nested PCR	L1	0	0	0	0	75	44	[56]
	Nested PCR, LIS-SSCP	L1	0	0	30	33	54	74	[57]
Hungary	PCR, southern blot hybridization technique	-	0	0	0	0	1	100	[58]

PCR: Polymerase chain reaction, HPV: Human papillomavirus, IHC: Immunohistochemistry, CRC: Colorectal cancer, E6: Envelop gene 6, E7: Envelop gene 7, L1: Long control region, LIS-SSCP: Low Ionic Strength-Single Strand Conformational Polymorphism, US: United States

respectively. In all case-control studies, the positivity ratios of HPV detection were higher in cancerous tissue samples as compared to the normal or benign controls. Based on the outcomes of these studies the most frequently identified HPV strains among the Iranian population were 16, 18, 55, and 56 HPV strains [Table 1].

Until now, in total, 05 studies^[32-36] including two^[34,36] case-control studies were conducted in Poland to find out the association of HPV with CRC. All these studies utilized the PCR technique for HPV detection with the help of E6, E7, and L1 gene specific-primers. The HPV detection positivity ratios reported in these studies were varied from 0% to 28%^[32] and 0%^[33,34] to 100%^[36] in normal/benign and cancerous tissue samples, respectively. In two case-control studies, the positivity ratio of HPV detection in cancerous tissue samples was higher than normal or benign. Based on the outcomes of these studies, the HPV strains 16 were the most frequently reported strain in the Polish population [Table 1].

A single case-control study^[37] has been performed in Hispania until now to determine the association of HPV with CRC. In which, a total of 36 benign and 45 cancerous tissues sample were screened using L1 gene-specific primers through the PCR technique. The results revealed the 2.8% and 42.2% HPV detection positivity ratio in benign and cancerous tissue samples. Based on the outcomes of this study, in the Hispanic population, HPV strain 16 was the most prevalent strain [Table 1].

In the United States (US), the association of HPV with CRC has so far been reported in 05 studies,^[18,38-41] including 3 case-control studies.^[18,39,40] These studies utilized the SPF10 INNO-LiPA, bead-based multiplex Luminex assay and PCR techniques for HPV detection with the help of primers, specific for E6, E7, and L1 region. The results of these studies showed the 0% HPV detection positivity in normal controls while 0%^[18,40] to 51%^[18] in cancerous

tissue samples. Based on the outcomes of these studies, HPV strain 16 was the most widely reported strain in the US population [Table 1].

In Italy, a total of 02 studies,^[42,43] including one case-control study^[43] have been conducted so far to establish the relationship between HPV and CRC. The Reverse blot hybridization and PCR technique were utilized by these studies for the identification of HPV. The results of these studies revealed the 8.8%^[43] HPV detection positivity ratio in benign tissues sample with varying frequencies of HPV detection positivity ratios ranging from 15.8%^[43] to 33.3%^[42] in cancerous tissue samples. Based on the outcomes of these studies, the HPV 16 and 18 were the most prevalent identified strains in the Italian population [Table 1].

In India, until now, there has been a single case-control study^[44] carried out to find out if HPV is associated with CRC or not. In total, 30 normal and 93 cancerous tissues sample were screened in that study through the PCR technique. They recorded 6% and 36.5% HPV detection positivity ratios in normal and cancerous tissue samples. According to the outcomes of this study, HPV strains 16 and 18 were the most prevalent strains in the Indian population [Table 1].

In total, 6 case-control studies^[12,45-49] analyzing the presence of HPV in CRC have been reported so far in China. Methodologies utilized by these studies for the detection of HPV include southern blotting hybridization and PCR technique. These studies calculated the HPV detections positivity ratios with different frequencies varied from 0%^[12,46] and 21.9%^[47] to 73%^[49] in normal/benign and cancerous tissue samples, respectively. In all these studies, the HPV detection positivity ratios were documented higher in cancerous tissues sample as compared to the normal and benign. Based on the outcomes of these studies, three different HPV strains (16, 6 and 33) were

the most frequently identified HPV strains in the Chinese population [Table 1].

A single study^[50] based on HPV etiology in CRC has been reported in Belgium until now. A total of 232 cancerous tissues sample were analyzed in this study by applying PCR technology, and they documented 14.2% HPV detection positivity ratio. Based on the outcomes of this study, HPV 16 was the most frequently identified strain in the Belgian population [Table 1].

A single case-control study^[19] has been conducted in Brazil so far to evaluate the presence of HPV in CRC. In this study, a total of 72 normal and 72 cancerous tissues sample were analyzed with the help of PCR using L1, E6, and E7 gene-specific primers. The Results of this study revealed 50% and 63.9% HPV detection positivity ratios in normal/benign and cancerous tissues sample, respectively. Based on the outcomes of this study, the most widely observed strains of HPV in the Brazilian population were 16, 18, and 31 [Table 1].

A couple of studies, including one case-control study^[51] have been reported in Taiwan so far, analyzing the HPV presence in CRC. In this study, a total of 19 cancerous tissues sample and 19 normal samples were screened through PCR and Southern blotting. The outcomes of this study showed the more HPV detection positivity ratios 84% in the normal sample, as compared to the cancerous tissue samples 53%. Based on the outcomes of these studies, the most commonly identified HPV strains in the Taiwan population were HPV strains 16 and 18 [Table 1].

A single case-control study^[39] was conducted in Israel to date to relate the HPV presence with CRC. In total, 30 normal and 106 cancerous tissues sample were screened in this study using L1 gene-specific primers through the PCR technique. The results of this study showed a 0% HPV detection positivity ratio in both normal and diseased samples [Table 1].

Until now, a single case-control study^[39] relating HPV with CRC has been reported in Spain. In total 30 normal and 100 cancerous tissues sample were analyzed in this study using L1 gene-specific primers through PCR technique, and none of the normal/benign and cancerous tissues samples were found positive for HPV [Table 1].

A total of 03 studies,^[53-55] including 2 case-control studies^[54,55] relating HPV with CRC have been reported so far in Turkey. Methodologies utilized in these studies include Reverse blot hybridization and PCR. The results of these studies showed the varying HPV detection positivity ratios ranging from 0%^[55] to 82.14%^[54] in cancerous tissue samples. Based on the outcomes of these studies, the HPV strains 18 and 33 were the most commonly identified strains in the Turkish population [Table 1].

Until now, a couple of studies have been reported in Argentina to find out the association between HPV and

CRC, out of them one was the case-control study^[57] in which a total of 54 cancerous tissues sample and 30 benign controls were examined by utilizing L1 gene-specific primers through nested PCR and Low Ionic Strength-Single Strand Conformational Polymorphism (LIS-SSCP). The results of this study revealed the 33% HPV detection positivity ratio in benign and 74% in cancerous tissues sample. Based on the outcomes of these studies, the HPV strains 6, 16, 18, 31, and 66 were the most commonly identified strains in the Argentine population [Table 1].

So far, in Hungary, a single study^[58] has been reported relating HPV with CRC. In this study, a single cancerous tissue sample was analyzed through PCR and southern blot hybridization, and results revealed the 100% HPV 16 detection positivity ratio [Table 1].

Discussion

In the present study, a total of 40 original research articles based on the HPV etiology in CRC from 16 different populations were examined. For this purpose, the required information obtained after an in-depth analysis of the extracted articles was population-wise categorized [Table 1]. Comparison between the methodologies used for the HPV detection and demonstration if the detection of the viral markers is more frequent in cancerous tissues samples as compared to the normal and benign samples and either the results of the summarized studies follow the Bradford hill postulates of causation or not were proposed as the main criteria of the present study for proving HPV etiology in CRC.

The results of this study are controversial since they fail to demonstrate the potential involvement of HPV in CRC development. In 1988, Boguszaková *et al.*^[24] were the first to analyze the HPV presence in 10 colon cancer samples through the southern blot hybridization technique. They found no evidence of HPV detection in the analyzed samples.

In 1992, Shah *et al.*^[38] conducted an analysis of HPV detection in 50 CRC patients from the US through the PCR technique. Similar to the previous study, no HPV markers were detected in the analyzed samples.

Since then, various studies have been carried out for the detection of HPV in CRC, some of them failed to detect the HPV in CRC, while others identified the HPV presence with different positivity ratios, varying between 0% and 100%. In a few case-control studies, the positivity ratios of HPV detection were higher in normal and benign samples as compared to the cancerous tissue while in other cases, the positivity ratios of HPV detection were also documented higher in cancerous tissues as compared to the normal or benign tissues. The reasons for such population-specific inequalities in HPV detection positivity ratios may include differences in socially controllable factors such as participation in the screening tests and

health-seeking behavior, as well as differential access to health services such as cancer treatment. Genetic and other “nonmodifiable” biological factors may also contribute to the existing inequalities.

The HPV positivity ratio pattern in cancerous and normal or benign tissue samples do not meet the requisite criteria and some of Bradford hill postulates of causation^[61] including (strength, consistency, and specificity) to declare the HPV as a potential biomarker of the CRC. However, the limitations and some issues with all the summarized studies related to the possibility of false-positive and false-negative results have been discussed below.

Possible causes of the false-negative results

Few studies found no evidence of HPV presence in any of their CRC samples they have analyzed. How can we be sure that the negative results were not due to the poor quality of the DNA? Many studies utilized positive control to avoid such situations,^[25-28,30] but two studies^[24,45] did not utilize the positive control so there is no way to confirm their negative results. The risk of contamination can never be ruled out in a PCR reaction that could significantly contribute to false-negative results. Few studies have used conventional PCR (25, 28, 33, 38, 39, 55) in which the risk of contamination is higher as compared to other studies using quantitative or real-time PCR (qPCR). Inappropriate selection of PCR primers for HPV detection could also result in false-negative results, for example, the primers used for L1 region may be unreliable for the detection of HPV in tissues of advanced carcinomas, as L1 and E1 regions may be lost during the integration of viral genome into the host genome, whereas the E6/E7 regions remained consistently present, so this is the plausible explanation for the completely negative results of^[25,28,34,39,55] studies.

Possible causes of the false-positive results

For the optimization of DNA amplification from digested tissues, many studies^[18,19,27,29,37,52,56] utilized nested PCR, a method that is prone to contamination and leads to false-positive results. Even though they cited good laboratory practices, so contamination was unlikely but cannot be completely ruled out. Vuitton *et al.*^[62] found the presence of HPV 16 DNA in 3/210 CRC samples, but confirmation of these positive cases by INNO-LiPA™ revealed that none of the samples was further positive for HPV 16 DNA. The presence of extracellular viruses in the colorectal tissue section can be a nonepithelial source of positive results.

Comparison of normal, benign and malignant samples

Case-control studies are needed to establish a link between the causative agent and the disease. Most of the investigations that we summarized^[24,26,29,31,33,35,38,41,42,50,52,53,56,58] only examined the malignant tissues that do not allow a comparison between cancerous and

normal or nonmalignant tissues. However, some studies^[12,18,19,25,27,30,34,36,37,39,40,43-47,49,51,54,55,59] examined both cancerous and normal or benign tissue samples. In some cases, this comparison demonstrated a higher HPV detection positivity in malignant tissues [Table 1] as compared to the normal or benign tissue samples, while in other cases, the opposite effect was also documented. However, none of the studies reported the association of HPV with a specific subtype and histological grade of CRC.

Conclusion

The results of the present study are controversial as they failed to prove the role of HPV as a potential participant in CRC but rather suggested it as cause-effective or at least a co-participant in the pathogenesis of CRC. However, additional pieces of evidence are required to obtain to prove HPV etiology in CRC.

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Conflicts of interest

There are no conflicts of interest.

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