Human Papillomavirus Infection and Oropharyngeal and Gastrointestinal Cancers: A Causal Relationship?

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Abstract: The human papillomavirus (HPV) is one of the most common sexually transmitted infections worldwide. The risk of being infected at least once in a lifetime among both men and women is estimated to be 50%. Although the majority of HPV infections are asymptomatic and improve within 2 years, approximately 10% of individuals develop a persistent infection and have an increased risk of developing carcinomas. The association of HPV and genital cancer is well established. However, there is evidence that HPV may also be associated with other cancers, including those of the gastrointestinal system. The aim of this review is to organize the current evidence of associations between HPV infections and oropharyngeal and gastrointestinal cancers, including the following: oropharyngeal, esophageal, gastric, colorectal, and anal cancers. A comprehensive review of the most up-to-date medical literature concluded that an HPV infection might have a role in the oncogenesis of gastrointestinal tract cancers. HPV may have a causal relationship with oropharyngeal and esophageal squamous cell cancers. However, the association between HPV and gastric and colorectal cancers is weaker. The development of cancer in the oropharyngeal and gastrointestinal tract is usually multifactorial, with HPV having a role in at least a subset of these cancers. HPV infections pose a big challenge due to their burden of infection and their oncogenic potential.

Keywords: human papillomavirus; oropharyngeal cancer; esophageal cancer; gastric cancer; colorectal cancer; anal cancer

1. Description of the Human Papillomavirus (HPV)

The human papillomavirus (HPV) is a small, non-enveloped, double-stranded DNA virus belonging to the papillomavirus family. HPV is one of the most common sexually transmitted infections worldwide. The risk of being infected at least once in a lifetime among both men and women is estimated to be 50% [1]. The transmission of HPV is through personal contact. Anogenital warts are commonly sexually transmitted. The age of onset of an HPV infection is similar to that of other sexually transmitted diseases (STDs). Additionally, individuals with HPV have higher frequencies of STDs, and having a large number of sexual partners is associated with a greater risk of condylomata acuminata [2]. However, minor trauma at the site of infection may also have a role since HPV incidence is higher among meat handlers, such as butchers. Young children may also acquire the virus from hand contact with non-genital lesions. Observations suggest that the disease may be transmitted through vaginal delivery and in utero via ascending infection from the mother’s genital tract [3].

HPV has an established oncogenic potential and is a major cause of infection-related cancers worldwide. HPV is diagnosed in more than 90% of cervical cancers and is currently the most common pathogen responsible for cancers in women [4]. Besides cervical cancers, HPV infections have been reported to potentially be associated with 90–93% of anal cancers,
12–63% of oropharyngeal cancers, 36–40% of penile cancers, 40–64% of vaginal cancers, and 40–51% of vulvar cancers [5]. The oncogenic potential of HPV varies according to genotype; the most common genotypes of HPV are 16 and 18, which are among the high-risk genotypes (Table 1). Both HPV type 16 and HPV type 18 are vaccine-preventable [1].

Table 1. Human papillomavirus genotypes and their oncogenic risks [6,7].

| Genotypes   | Characteristics                                                                 |
|-------------|---------------------------------------------------------------------------------|
| High risk   | 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82                      |
|             | They are associated with cancers.                                                |
| Low risk    | 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 81                                      |
|             | They cause benign lesions affecting the anogenital areas, such as genital warts (condylomata), low-grade squamous intraepithelial lesions of the cervix, and laryngeal papillomas. |

HPV infections, especially with high-risk genotypes, have been recently associated with gastrointestinal cancers. Although direct evidence is lacking and the results of the studies are inconsistent, serologic and histologic studies suggest a possible association.

2. HPV and Oncogenesis

Oncogenic HPVs are sexually transmitted, and the infection (typically cervical) can result in mild cytological abnormalities [8]. For the majority of people (around 90%), it improves within 2 years. In a small group of patients, it causes long-term persistent infections, leading to cervical intraepithelial neoplasia (CIN). The oncogenic progression from CIN1 to CIN3 may lead to invasive cervical cancer. It is estimated that one third of CIN3 can progress to cancer within 10 to 20 years [8].

The HPV proteins E6 and E7 have a critical role in HPV-induced cellular immortalization, transformation, and carcinogenesis [9]. Both E6 and E7 express their oncogenic activity primarily through protein–protein interactions with tumor suppressor proteins. The tumor suppressor p53 has a role in preventing the development of cancer. In healthy cells, p53 levels are kept low by degradation via the ubiquitin ligase Mdm2 [10]. Alterations of p53 are common in cancer. The E6 oncoprotein of HPV forms a ternary complex with the cellular E3 ubiquitin ligase E6AP and p53, leading to ubiquitin-mediated degradation of p53 and a subsequent decrease in its cellular levels [11,12]. A common polymorphism occurring in the p53 amino acid sequence results in the presence of either a proline or an arginine at position 72 and increases the susceptibility of p53 to E6-mediated degradation [11,13]. The E7 protein binds to the retinoblastoma protein 1 (RB1) and provides its inactivation, leading to cell-cycle progression through the activation of E2F-driven transcription [14].

During the persistent infection, the virus is presumably not detected by the immune system [15]. Since the viral activity is mainly in the upper cell layers, the virus may escape the immune responses. In addition, HPV interferes with the innate immune responses and has the ability to delay the adaptive immune responses [15]. An HPV infection follows a latent course, and thereafter it may reactivate. Re-infection is possible even with the same HPV type, especially in women who previously did not seroconvert, suggesting the protective role of humoral immunity [8]. The role of the immune system in controlling HPV infections and subsequent cancer development is evident in individuals with immunosuppression. Patients with Fanconi’s anemia have DNA repair defects and are more susceptible to HPV-related cancers [16].

Chronic inflammation of the digestive system by an HPV infection seems to cause long-term complications. However, an infection with a non-cancerogenic HPV type may provide protection from the cancerogenic types through cross-reactivity, epitope spreading, and de novo immune stimulation [17].
3. Human Papillomavirus and Gastrointestinal Cancers

There is a clear association between HPV and genital cancers. Additionally, there is evidence that HPV may have a role in the oncogenesis of oropharyngeal and anal cancers. Increasing epidemiological information suggests that even other gastrointestinal cancers may have an association with HPV. The medical literature is complicated by the sample size, the detection method for HPV, and the definition of a control group among studies. The HPV detection methods, the specimens used, and the advantages and disadvantages of the methods are given in Table 2.

Table 2. Human papillomavirus detection methods [18–20].

| Detection of HPV Proteins                  | Specimen                        | Advantage                                      | Disadvantage                                      |
|-------------------------------------------|---------------------------------|-----------------------------------------------|----------------------------------------------------|
| Immunohistochemistry                      | Fresh-frozen samples, FFPE      | High experience, commonly used, high sensitivity | Low specificity, time consuming, technically cumbersome |
| Western blot                              | Fresh-frozen samples            | Moderate to high specificity                   | Low sensitivity, time consuming, technically cumbersome |
| Detection of HPV genomes                  |                                 |                                               |                                                    |
| Southern blot                             | Fresh-frozen samples            | Moderate to high sensitivity and specificity   | Not easily performed to FFPE tissues               |
| In situ hybridization                     | FFPE, fresh samples             | Moderate sensitivity and specificity           | Requires DNA and tissue preservation               |
| Signal amplification (hybrid capture)     | Fresh-frozen samples, FFPE      | High sensitivity and specificity, provides viral load information | No typing provided                                |
| PCR                                       | Fresh-frozen samples, any bodily fluid | Very high sensitivity, low specificity | Does not provide quantitative measurement of viral load |
| Real-time PCR                             | Fresh-frozen samples, FFPE tissues, any bodily fluid | Very high sensitivity and specificity | Labor-intensive                                   |
| Detection of antibodies against HPV       | Serum                           | Easy to perform                                | Sensitivity and specificity are low                |

PCR, polymerase chain reaction; FFPE, formalin-fixed and paraffin-embedded.

3.1. HPV and Oropharyngeal Cancer

Oropharyngeal cancer (OPC) includes tumors that arise from the oral cavity, oropharynx, larynx, hypopharynx, and sinonasal tract. The main risk factors are male gender, prior tobacco use, and alcohol use [21]. About 90% of head and neck cancers are squamous cell carcinomas. HPV is suggested to have a role in oropharyngeal cancers, particularly in squamous cell carcinomas of the region.

While the incidence of head and neck cancers has decreased in the last few decades, the incidence of OPCs has increased and is largely attributable to the increase in HPV infections [22]. The prevalence of HPV-positive OPCs has increased from approximately 47% in 2000 to approximately 74% in 2012 in Canada [23]. It has also increased by 225% between 1988 and 2004 and now comprises up to 90% of all new cases of OPCs in the United States [24]. Current evidence shows a causal relationship between oropharyngeal squamous cell carcinoma (SCC) and HPV. The high-risk HPV types 16 and 18 appear to be the cause of the rising rate of SCCs [22–24]. The patients’ characteristics also have changed; the patients are often younger and healthier with a high socioeconomic status and with minimal to no smoking history, in contrast to the traditional older patient with a long history of tobacco and alcohol use [25]. Compared to HPV-negative OPCs, after treatment, HPV-positive OPCs are associated with a more favorable prognosis.
HPV-positive OPCs have a male predominance; their incidence in men is three to five times higher than in women worldwide [26]. More than 90% of HPV-positive OPCs are caused by the high-risk HPV genotype 16 [26].

3.2. HPV and Esophagus Cancer

Esophageal carcinoma (EC) is one of the most aggressive malignant cancers of the gastrointestinal tract. Multiple risk factors are defined for the carcinogenesis, including alcohol and tobacco use, nutritional deficiencies, and infectious agents [27]. HPV infections have been recently reported as another possible risk factor for the development of ECs.

There are conflicting results in the studies investigating the role of HPV. The studies mainly compared tissues with cancer to surrounding normal tissues and studied HPV by PCR or immunochemistry [28–71] (Table 3). Among the studies, 28 out of 44 (64%) reported that HPV positivity is significantly higher in esophageal cancer patients, including the studies enrolling the highest number of patients [33,55,60,67,69]. We included studies with all histologic types. Studies that focused on esophageal squamous cell carcinomas (ESCCs) suggested a stronger association as follows: an analysis of eight meta-analyses studying the role of HPV reported that the meta-analyses included between 1223 and 13,832 patients with ESCCs and the overall percentage of HPV-positive ESCC cases ranged from 11.7% to 38.9%. The analysis reported that geographic location accounts for a majority of the variations in HPV prevalence; high-incidence regions, including Asia, reported significantly higher HPV–ESCC infection rates compared to low-incidence regions, such as Europe, North America, and Oceania [72].

Table 3. Summary of the studies on the human papillomavirus in esophageal cancer.

| Reference         | Country       | Year | HPV (+) in Cancer Patients | HPV (+) in Control Group | p * | HPV Detection Method | HPV Types Studied |
|-------------------|---------------|------|----------------------------|--------------------------|-----|----------------------|-------------------|
| Astori, G., et al. [28] | Italy         | 2001 | 7/17                       | 4/16                     | NS  | PCR                  | 16                |
| Acevedo, N.E., et al. [29] | Mexico        | 2004 | 15/17                      | 4/23                     | <0.00001 | PCR | 11,16,18            |
| Bahnassy, A.A., et al. [30] | Egypt         | 2005 | 27/50                      | 12/50                    | <0.05 | PCR | 11,16,18,33         |
| Benamouzig, R., et al. [31] | France        | 1992 | 5/12                       | 1/24                     | <0.05 | ISH | 6,11,16,18,31,33    |
| Cao, B.W., et al. [32] | China         | 2005 | 207/265                    | 203/357                  | <0.00001 | PCR | 16,18              |
| Chen, J., et al. [33] | China         | 2004 | 14/30                      | 7/60                     | <0.001 | PCR | 16                |
| Chen, W.G., et al. [34] | China         | 2014 | 44/66                      | 8/66                     | <0.00001 | Gene chip technology | 16,18            |
| Cui, X., et al. [35] | Kazakhstan    | 2014 | 58/183                     | 8/89                     | <0.0001 | PCR | 6,11,16,18,35,43,52 |
| da Costa, A.M., et al. [36] | Brazil        | 2018 | 12/87                      | 12/87                    | NS  | PCR                  | 16                |
| Dabrowski, A., et al. [37] | Poland        | 2012 | 28/56                      | 4/35                     | NS  | PCR                  | 16,18             |
| Dong, H.C., et al. [38] | Kazakhstan    | 2015 | 46/89                      | 14/49                    | <0.00001 | PCR | 6,16,33,39,51,82    |
| Farhadi, M., et al. [39] | Iran          | 2005 | 14/38                      | 5/38                     | <0.05 | PCR | 16,18              |
| Georgantis, G., et al. [40] | Greece        | 2015 | 2/19                       | 0/30                     | NS  | PCR                  | 11,31             |
| Gessner, A.L., et al. [41] | Malawi        | 2018 | 6/40                       | 0/12                     | NS  | RT-PCR and ISH       | 16,18,31,45       |
| Han, C., et al. [42] | China         | 1996 | 22/90                      | 6/121                    | <0.0001 | ELISA | 16                |
| He, Z., et al. [43] | China         | 2014 | 366/1435                   | 213/2071                 | <0.00001 | ELISA | 16                |
| Jiang, H.Y., et al. [44] | China         | 2005 | 48/65                      | 11/65                    | <0.00001 | IHC | 16,18              |
| Kamangar, F., et al. [45] | China         | 2006 | 33/99                      | 106/381                  | NS  | ELISA                | 16,18,73          |
| Kawaguchi, H., et al. [46] | Japan, China  | 2000 | 17/75                      | 17/75                    | NS  | PCR                  | 16                |
| Kayamba, V., et al. [47] | Zambia        | 2015 | 2/44                       | 1/48                     | NS  | PCR                  | -                 |
| Khurshid, A., et al. [48] | Japan         | 1998 | 17/27                      | 3/12                     | <0.05 | PCR | 16,18,33            |
| Kuang, Z.S., et al. [49] | China         | 2000 | 23/56                      | 4/56                     | <0.0001 | PCR | 16,18              |
| Lagergren, J., et al. [50] | Sweden        | 1999 | 20/193                     | 61/302                   | <0.05 | ELISA | 16,18              |
### Table 3. Cont.

| Reference                  | Country      | Year  | HPV (+) in Cancer Patients | HPV (+) in Control Group | p *  | HPV Detection Method | HPV Types Studied |
|----------------------------|--------------|-------|-----------------------------|--------------------------|------|----------------------|-------------------|
| Li, Y., et al. [51]         | China        | 1991  | 12/24                       | 9/24                     | NS   | ISH                  | 16                |
| Liu, H.Y., et al. [52]      | China        | 2014  | 11/30                       | 60/78                    | <0.0001 | PCR                | 16                |
| Liu, J., et al. [53]        | China        | 2000  | 44/60                       | 23/56                    | 0.001 | IHC                 | 16,18             |
| Liyanage, S.S., et al. [54] | Australia    | 2014  | 1/99                        | 0/100                    | NS   | PCR-ELISA            | 16                |
| Lu, L.C., et al. [55]       | China        | 1999  | 15/55                       | 43/55                    | <0.00001 | ISH                | 18                |
| Lu, X.M., et al. [56]       | China        | 2004  | 55/104                      | 41/104                   | 0.051 | (NS) PCR             | 16                |
| Lyronis, I.D., et al. [57]  | Greece       | 2008  | 14/22                       | 3/14                     | <0.05 | PCR                 | 16,18             |
| Parameshwaran, K., et al. [58]| Australia     | 2019  | 6/41                        | 1/49                     | <0.05 | PCR                 | 16,18             |
| Rajendra, S., et al. [59]   | Australia    | 2020  | 3/26                        | 5/328                    | <0.001 | ELISA              | 6,11,16,18,31,33,45,52,58 |
| Ren, Z.H.P., et al. [60]    | China        | 1996  | 35/52                       | 2/30                     | <0.00001 | IHC                | 16,18             |
| Sadeghian, Z., et al. [61]  | Iran         | 2022  | 20/70                       | 0/70                     | <0.00001 | PCR                | 16,18             |
| Shen, Z.Y., et al. [62]     | China        | 2002  | 115/176                     | 105/176                  | NS   | PCR                 | 6,11,16,18        |
| Tornesello, M.L., et al. [63]| Italy        | 2009  | 12/56                       | 8/27                     | NS   | PCR                 | 6,8,15,16,20,25   |
| Wang, X.J., et al. [64]     | China        | 1998  | 20/40                       | 36/58                    | NS   | ISH                 | 16                |
| Wong, M.Y.W., et al. [65]   | Australia    | 2018  | 18/36                       | 6/55                     | <0.0001 | PCR                | 6,16,18          |
| Xu, C.L., et al. [66]       | China        | 2004  | 16/18                       | 126/183                  | NS   | IHC                 | 16                |
| Xu, W.G., et al. [67]       | China        | 2003  | 28/40                       | 10/50                    | <0.00001 | ISH                | 16                |
| Yahyapour, Y., et al. [68]  | Iran         | 2018  | 27/100                      | 28/68                    | 0.054 (NS) | Real Time PCR         | 16,18,35,39,45,56 |
| Yang, J., et al. [69]       | China        | 2014  | 170/313                     | 136/314                  | <0.01 | ELISA               | 16                |
| Zhou, S.M., et al. [70]     | China        | 2009  | 26/82                       | 10/80                    | <0.05 | PCR                 | 16                |
| Zhou, X.B., et al. [71]     | China        | 2003  | 31/48                       | 8/23                     | <0.05 | PCR                 | 16                |

* Chi-square test. NS, not significant; PCR, polymerase chain reaction; IHC, immunohistochemistry; ISH, in situ hybridization; ELISA, enzyme-linked immunosorbent assay.

The meta-analysis and the systematic review included 33 randomized studies with 6051 EC patients [73]. The HPV infection rate in the EC group was 46.5% (1131/2430), while it was 26.2% (977/3621) in the control group (OR = 1.62; 95% CI 1.33–1.98). This meta-analysis suggests that HPV infections and the incidence of ECs are closely associated.

### 3.3. HPV and Gastric Cancer

Gastric cancer (GC) is the sixth most common cancer in both sexes worldwide [74]. It is more prevalent in the male population in developing countries, mainly in East Asia, South America, and Eastern Europe. The etiological factors include the following: improper eating habits, a diet rich in cured and smoked meat products with low antioxidant content, tobacco smoking and alcohol consumption, and chronic *Helicobacter pylori* or Epstein–Barr virus (EBV) infections [75,76]. The role of HPV in the oncogenesis of gastric cancer has been investigated in a few studies.

A meta-analysis published in 2016 investigated the HPV and gastric carcinoma association [77]. It included 30 studies with 1917 patients with GC and 576 controls. It found the pooled HPV prevalence to be 28.0%. Based on 15 case control studies, the pooled odds ratio was found to be 7.388. The meta-analysis found that the HPV prevalence was significantly higher in patients from China than in those from non-Chinese regions (31% vs. 9%, p < 0.001). The pooled prevalence of HPV 18 was found to be 7% and HPV 16 was found to be 21% in GC tissues. HPV 16 was detected as being three times more prevalent than HPV 18.

Another recent meta-analysis studied the role of HPV in GC [78]. It included 14 studies investigating the prevalence of HPV in 901 gastric carcinoma patients and 1205 controls. The pooled HPV prevalence in gastric carcinoma was found to be 23.6%. An association between an HPV infection and a risk of GC was observed (odds ratio = 1.53). In this
meta-analysis, noncancerous, healthy, and benign gastric diseases were used as controls, and the prevalence of HPV in patients with GC was significantly higher than that in the paired corresponding normal tissue controls. The association between an HPV-16 infection and a risk of gastric cancer was statistically significant (OR = 2.42).

HPV type 16 infection seemed to increase the risk of GC. However, since GC oncogenesis is multifactorial and it is not clear whether the effect of HPV is due to its oncogenic potential or whether it is the consequence of chronic inflammation; a causal relationship remains to be established. It is not clear whether the prognosis for HPV-positive GC differs from the HPV-negative one.

3.4. HPV and Colorectal Cancer

Colorectal cancer (CRC) is the second most common cancer in women and the third most common one in men [79]. The risk factors are reported as heredity (genetic factors), lifestyle factors, such as high consumption of red meat, or tobacco smoking [80]. HPV can infect the colorectal region via an ascending infection from anogenital sites or through hematogenous or lymphatic spread. HPV has been suggested as a potential risk factor for the development of CRCS. Many studies investigated the presence of HPV in colorectal cancer tissues and compared them to normal and surrounding tissues (Table 4) [81–111]. In the majority of cases, the prevalence of HPV in cancer tissue has been higher than that in the control, suggesting a role for HPV in the oncogenesis of CRC.

Table 4. Summary of the studies on the human papillomavirus in colorectal cancer.

| Reference | Country   | Year | HPV Positivity in Cancer Tissues | HPV Positivity in Control Tissues | p*  | Detection Method                      | HPV Types Studied |
|-----------|-----------|------|---------------------------------|----------------------------------|-----|--------------------------------------|-------------------|
| Aghakhani, A., et al. [81] | Iran      | 2014 | 0/70                            | 0/30                             | NS  | PCR                                  | >20 types         |
| Audeau, A., et al. [82]       | New Zealand | 2002 | 20/2351                         | 0/20                             | NS  | IHC                                  | 6,11,16,18        |
| Bernabe-Dones, R.D., et al. [83] | USA     | 2016 | 19/45                           | 1/36                             | <0.0001 | nested PCR                           | 6,11,16,18        |
| Bodaghi, S., et al. [84]      | USA       | 2005 | 28/55                           | 0/10                             | <0.01 | PCR                                  | >20 types         |
| Boguszakowá, L., et al. [85]  | Czechia   | 1998 | 0/13                            | 0/10                             | NS  | Southern blot hybridization          | 2,6,16,18         |
| Buyru, N., et al. [86]        | Turkey    | 2006 | 43/53                           | 17/53                            | <0.0001 | PCR                                  | 6,11,16,18,33    |
| Cheng, J.Y., et al. [87]      | China     | 1995 | 37/70                           | 11/37                            | <0.05 | PCR and southern blot                | 6,11,16,18,33    |
| Dalla Libera, L.S., et al. [88] | Brazil | 2020 | 13/79                           | 0/75                             | <0.001 | PCR                                  | 32 types          |
| Gazzaz, F., et al. [89]       | Saudi Arabia | 2016 | 2/60                            | 2/72                             | NS  | Digene procedure                     | 18 types          |
| Gornick, M.C., et al. [90]    | USA       | 2010 | 0/279                           | 0/30                             | NS  | PCR reverse line blot and the SPF10 INNO-LiPA | 39 types         |
| Hafez, F.S., et al. [91]      | Egypt     | 2022 | 13/59                           | 0/30                             | <0.01 | IHC                                  | -                 |
| Kirgan, D., et al. [92]       | USA       | 1990 | 42/43                           | 25/60                            | <0.0001 | In situ DNA hybridization           | 6,11,16,18,31,33,35 |
| Laskar, R.S., et al. [93]     | India     | 2015 | 34/93                           | 6/30                             | NS  | PCR                                  | 16,18             |
| Lee, Y.M., et al. [94]        | Taiwan    | 2001 | 16/19                           | 10/19                            | <0.05 | PCR and southern blot                | 18                |
| Li, Y.X., et al. [95]         | China     | 2015 | 46/95                           | 29/100                           | <0.01 | HPV Genotyping Chip technology and IHC | 23 types         |
| Liu, F., et al. [96]          | China     | 2011 | 32/96                           | 0/32                             | <0.0001 | PCR                                  | 21 types          |
| Mahmoudvand, S., et al. [97]  | Iran      | 2015 | 2/70                            | 4/140                            | NS  | PCR                                  | 16,18             |
| McGregor, B., et al. [98]     | USA       | 1993 | 13/38                           | 10/45                            | NS  | PCR and southern blot                | 6,11,16,18,33    |
| Miliello, V., et al. [99]     | Italy     | 2009 | 2/72                            | 0/72                             | NS  | PCR                                  | >20 types         |
| Nagi, K., et al. [100]        | Lebanon   | 2021 | 60/94                           | 4/13                             | <0.05 | PCR                                  | 14 types          |
| Pérez, L.O., et al. [101]     | Argentina | 2005 | 40/54                           | 10/30                            | <0.001 | PCR                                  | >20 types         |
Table 4. Cont.

| Reference                         | Country     | Year | HPV Positivity in Cancer Tissues | HPV Positivity in Control Tissues | p       | Detection Method                      | HPV Types Studied |
|-----------------------------------|-------------|------|----------------------------------|-----------------------------------|---------|---------------------------------------|-------------------|
| Picanço-Junior, O.M., et al. [102]| Brazil      | 2014 | 36/79                            | 5/65                              | <0.00001| PCR                                  | 19 types          |
| Ranjbar, R., et al. [103]         | Iran        | 2014 | 5/80                             | 1/80                              | NS      | nested PCR                           | >20 types         |
| Salepci, T., et al. [104]         | Turkey      | 2009 | 46/56                            | 18/56                             | <0.0001 | PCR and southern blot hybridization   | 6,11,16,18,33     |
| Snietura, M., et al. [105]        | Poland      | 2012 | 0/10                             | 0/40                              | NS      | qPCR                                 | 14 types          |
| Soto, Y., et al. [106]            | Cuba        | 2016 | 10/24                            | 5/39                              | <0.01   | qPCR                                 | 16,18,31,33,45,52,58|
| Taherian, H., et al. [107]        | Iran        | 2014 | 0/50                             | 0/50                              | NS      | PCR                                  |                   |
| Tanzi, E., et al. [108]           | Italy       | 2015 | 9/57                             | 5/57                              | NS      | Degenerate PCR                       | 16,18,33,58       |
| Vuitton, L., et al. [109]         | France      | 2017 | 0/210                            | 0/40                              | NS      | qPCR                                 | 16 types          |
| Zhang, J., et al. [110]           | China       | 2005 | 42/82                            | 4/82                              | <0.0001 | PCR                                  | 16 types          |
| Zhu, Q., et al. [111]             | China       | 1999 | 20/46                            | 0/16                              | <0.01   | PCR                                  | 6,11,16,18,33     |

* Chi-square test. NS, not significant; PCR, polymerase chain reaction; qPCR, quantitative PCR; IHC, immunohistochemistry.

The correlation between HPV and CRC was analyzed using the Hill criteria [112]. The analysis revealed some evidence for analogy, biological plausibility, and strength of association but only weak evidence for consistency, specificity, and coherence. Two meta-analyses suggested a significant increase in the risk of CRC development with the presence of HPV [113,114]. However, the sample sizes were small and the HPV detection methods varied among studies.

Among 32 controlled studies, 17 (53%) found a higher prevalence of HPV in colorectal cancer patients. Studies involving the highest numbers of patients were among those finding no significant differences [84,98,105]. The current evidence shows an increased risk, and further information is needed to establish a causal relationship. There is no information on the clinical outcomes of HPV-associated colorectal tumors.

3.5. HPV and Anal Cancer

The majority of anal cancers (89–100%) are induced by long-term HPV infections [115]. Anal cancer comprises 4% of all malignancies of the lower alimentary tract. Its incidence is increasing in high-income countries, and its incidence is higher in women than in men [113]. The risk groups for anal cancer have been identified as men who have sex with men, transplant recipients, people living with HIV or AIDS infections, and women with a history of HPV-induced cervical, vaginal, or vulvar cancer [115].

There are an estimated 27,000 new cases of anal cancer every year worldwide, with the ratio of female to male cases being as high as 5:1 [116]. White women have higher rates of anal squamous cell carcinomas compared to black women. On the other hand, black men have a significantly higher incidence of anal cancer than white men [117].

HPV infections are not necessarily transmitted directly to the anus; they can spread from one area to another. They can extend from the genitals to other organs. They can be transmitted not only through sexual intercourse (vaginal, anal, or oral), but also via hand-to-genital contact. Many HPV-infected individuals may not have genital warts or other signs of infection [116]. During an active HPV infection, patients may present with common warts, planar warts, flat warts, anal dysplasia, or oropharyngeal lesions. In particular, there can be genital warts with various appearances, including flat, raised, single, or multiple.

There may be no symptoms in 20% of individuals, but the majority of individuals can present symptoms, including fissures, hemorrhoids, dermatitis of the anal region, pain in the anal region, loss of bowel control, and anorectal fistulas with discharge [118]. A growing mass in the anal canal may appear later, or the patient may present with inguinal lymphadenopathy due to metastasis.
There appears to be a higher prevalence of HPV in patients with oropharyngeal and gastrointestinal cancers, suggesting a role for HPV in the oncogenesis of gastrointestinal tract cancers. In parallel to the urogenital cancers, the prevalent HPV types are 16 and 18 in oropharyngeal and gastrointestinal cancers (Table 5).

Table 5. Prevalent HPV types in urogenital and gastrointestinal cancers [6,7].

| HPV Type                        | Urogenital cancers                                                                 | Gastrointestinal cancers |
|---------------------------------|-------------------------------------------------------------------------------------|--------------------------|
|                                 | 16 (squamous cell carcinomas), 18 (adenocarcinomas), 45,31,33,52,58,35               |                          |
| Oropharyngeal cancers           | 16 (>90%)                                                                           |                          |
| Esophageal cancers              | 16,18                                                                               |                          |
| Gastric cancers                 | 16,18                                                                               |                          |
| Colorectal cancers              | 16,18,31,33                                                                         |                          |
| Anal cancers                    | 16 (80%), 18                                                                         |                          |

In squamous oropharyngeal and squamous esophageal cell cancers, the current evidence points to a causal relationship. In gastric and colorectal cancers, the association seems weaker. The development of cancer in the oropharyngeal and gastrointestinal tract is usually multifactorial; HPV may have a role in at least a subset of these cancers. HPV infections pose a big challenge due to their burden of infection and oncogenic potential. The HPV strains that might be involved in the oncogenesis of oropharyngeal and gastrointestinal tract cancers are vaccine-preventable. HPV vaccination is key not only to the prevention of urogenital cancers but also, at least in part, of oropharyngeal and gastrointestinal tract cancers, since the study of the bivalent HPV 16/18 vaccine in women showed that cervical, anal, and oral infections could be prevented [119]. The screening of clinical samples of the oropharyngeal and gastrointestinal systems for HPV can provide more information about the relationship and provide the detection of HPV-positive individuals. The relatively higher prevalence of HPV among patients with oropharyngeal and gastrointestinal cancers should be further investigated by basic and clinical studies to clarify any causal relationship.

4. Conclusions

Persistent HPV infections induce the development of cancer. While a clear association has been established with urogenital cancers, the current evidence also points to a causal relationship with squamous oropharyngeal and squamous esophageal cell cancers. For gastric and colorectal cancers, HPV may have a role, although the association is weaker.

The most prevalent HPV types, 16 and 18, in urogenital cancers are also prevalent in oropharyngeal and gastrointestinal cancers. Since these types are vaccine-preventable, HPV vaccination is the optimal strategy to prevent HPV-related cancers, including urogenital cancers and at least a certain part of oropharyngeal and gastrointestinal tract cancers. The relatively higher prevalence of HPV among patients with oropharyngeal and gastrointestinal cancers should be further studied. The screening of clinical samples of the oropharyngeal and gastrointestinal systems for HPV can provide the greatest number of patients to obtain more conclusive information.

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