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ORIGINAL ARTICLE / *ARTIGO ORIGINAL*

Colorectal cancer prevalence linked to human papillomavirus: a systematic review with meta-analysis

Prevalência de câncer colorretal associado ao papilomavírus humano: uma revisão sistemática com metanálise

Thaisa Pelizzer[I], Caroline Pieta Dias[II], Julia Poeta[I,II], Tânia Torriani[I,III], Cristian Roncada[I,IV]

ABSTRACT: ***Introduction:*** Colorectal cancer is one of the most prevalent types of tumors worldwide. Deaths caused by these malignant tumors remain high and have stayed practically at the same level for the last few decades. Among the established risk factors for the development of cancer are infections due to pathogens or viruses. Among the viruses, the human papillomavirus (HPV) is the most prevalent, with over 180 strains, 40 of which are directly related to anogenital infections. ***Objective:*** Systematically assess the main studies which link HPV to colorectal cancer with meta-analysis. ***Methods:*** The search strategy adopted was the logic based on specific descriptors (English language), in combination with the Boolean operators (AND/OR). The search was conducted in the following databases: PubMed, ScienceDirect, and Scientific Electronic Library Online (SciELO), between April and May 2015. ***Results:*** 1,549 samples were assessed, with 956 (61.7%) being males. Six hundred thirty out of 1,358 cases of colorectal cancer due to HPV were diagnosed (51.9%). From these, 408 of 767 (51.9%) were male and 404 of 598 (67.5%) were linked to HPV 16 and 18, with tumor prevalence in the area of the cervix (253 of 411; 61.3%). From the total of 598 samples for the prevalence estimate of HPV 16 and 18, the number of cases with similar numbers was 204 (31.7%) and 200 (35.8%), respectively. Relatively significant numbers were found in the area of the cervix, 253 (61.3%), and the area of the rectum, 158 (38.7%). ***Conclusion:*** After conducting the present study, the link between HPV and colorectal cancer was made evident, without a distinction between the sexes, with similar values between HPV 16 and HPV 18.

Keywords: Colorectal cancer. Human papillomavirus. HPV 16. HPV 18. Prevalence. Epidemiology.

[I] *Faculdade da Serra Gaúcha* – Caxias do Sul (RS), Brazil.
[II] *Universidade Federal do Rio Grande do Sul* – Porto Alegre (RS), Brazil.
[III] *Universidade Feevale* – Novo Hamburgo (RS), Brazil.
[IV] *Pontifícia Universidade Católica do Rio Grande do Sul* – Porto Alegre (RS), Brazil.
Corresponding author: Cristian Roncada. Rua Os Dezoito do Forte, 2.366, Pio X, Caxias do Sul, RS, Brazil. E-mail: crisron@gmail.com
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RESUMO: ***Introdução:*** O câncer colorretal é um dos tipos de tumor mais prevalentes na população mundial. A mortalidade causada por esses tumores malignos continua elevada e mantém-se praticamente no mesmo nível nas últimas décadas. Entre os fatores de risco já estabelecidos para o desenvolvimento do câncer estão as infecções por patógenos ou vírus. Entre os vírus, o papilomavírus humano (HPV) é o mais prevalente, tendo mais de 180 cepas, das quais 40 estão diretamente relacionadas com infecções anogenitais. ***Objetivo:*** Avaliar de forma sistemática, com metanálise, os principais estudos que associam o HPV ao câncer colorretal. ***Métodos:*** Como estratégia de busca foi adotada a lógica baseada em descritores específicos (idioma inglês), vinculados aos operadores booleanos (*AND/OR*). As buscas foram aplicadas nas bases de dados PubMed, ScienceDirect e *Scientific Electronic Library Online* (SciELO), no período de abril e maio de 2015. ***Resultados:*** Foram avaliadas 1.549 amostras, sendo 956 (61,7%) do sexo masculino. Foram diagnosticados 630/1.358 casos de câncer colorretal por HPV (51,9%). Destes, 408/767 (51,9%) eram do sexo masculino e 404/598 (67,5%) foram associados aos HPVs 16 e 18, com prevalência tumoral na região do colo (253/411; 61,3%). Do total de 598 amostras para estimativa das prevalências de HPV-16 e HPV-18, a quantidade de casos com valores muito semelhantes foi de 204 (31,7%) e 200 (35,8%), respectivamente. Foram verificados valores relativamente expressivos na região do colo, 253 (61,3%), e na região retal, 158 (38,7%). ***Conclusão:*** Após a realização do presente estudo, a associação entre HPV e câncer colorretal ficou evidente, não havendo distinção entre gêneros, com valores muito semelhantes entre o HPV-16 e o HPV-18.

Palavras-chave: Câncer colorretal. Papilomavírus humano. HPV-16. HPV-18. Prevalência. Epidemiologia.

INTRODUCTION

Human papillomavirus (HPV) infection has come to be considered the most frequent worldwide. In the last two decades, studies conducted in China, the United States, Turkey, Belgium, Iran, Argentina, Peru, and Brazil (Table 1) have been indicating the concern with the number of new cases (incidence of the disease), a phenomenon that tends to rise significantly throughout the years, both in men and women, due to the elevated number of partners, homosexual relations, hygiene practices, smoking, and poor attention to protection during sexual contact[1].

There are currently over 180 types of cancer, each with specific clinical and biological characteristics, those of which should be assessed for accurate diagnosis and adequate treatment of the disease[1]. Cancer is a disorder that is characterized by the loss of control over cellular division and the capacity to invade other organic structures[2]. Invasive cancer neoplasia corresponds to this form of non-controlled cellular growth, known as "malignant tumors[3]."

Despite the advances in diagnosis and treatment, deaths caused by these tumors continue to be high and have remained at the same level for the last four decades[4]. Average overall survival in the last five years has been described as around 55% for developed countries and 40% for countries in development[5].

Colorectal cancer is one of the most prevalent worldwide[6]. In the United States, the disease is the third most diagnosed neoplasia[7], whereas in Brazil it is among the six most

prevalent types of cancer[8]. The most common symptoms are changes in bowel habits, weight loss, abdominal pain, hematochezia, and anemia[9]. Most colorectal cancers develop slowly and gradually[10]. Infections through pathogens or viruses are among the risk factors for the development of this cancer[11]. It is estimated that at least 50% of sexually active individuals will come in contact with HPV at some point in their lives[9]. Regarding men and women in Brazil, the prevalence varies between 35 and 72%, with high-risk HPVs being responsible for 25–56% of cases. When the precancerous lesions and lesions linked to cancer are assessed, it is observed that HPV 16 and 18 are responsible for approximately 55% of the cases with high-risk lesions and around 70% of cases of cervical cancer, both in South America and in Brazil[8].

Another risk factor is the genetic predisposition, such as familial adenomatous polyposis or first degree relatives with colorectal cancer[12]. In addition, environmental factors

Table 1. Overall characteristics of the assessed studies in the systematic review.

Author	Year	Location	n	Diagnostic Test
Bodaghi et al.[19]	2005	USA	55	PCR
Buyru et al.[20]	2006	Turkey	53	PCR/Southern blot
Chen et al.[21]	2012	China	69	PCR/Hybridization ISH
Cheng et al.[22]	1995	China	70	PCR/Southern blot hybridization
Damin et al.[23]	2007	Brazil	76	PCR
Deschoolmeester et al.[24]	2010	Belgium	232	PCR
Giuliani et al.[25]	2008	Turkey	66	PCR
Karbasi et al.[26]	2015	Iran	38	PCR
Liu et al.[27]	2010	China	96	PCR
Pérez et al.[28]	2006	Argentina	53	PCR
Pérez et al.[29]	2010	Argentina	75	PCR
Picanço-Júnior et al.[30]	2014	Brazil	144	PCR
Quinn et al.[31]	2012	Peru	105	PCR
Ranjbar et al.[32]	2014	Iran	160	PCR
Salepci et al.[33]	2009	Turkey	56	PCR/Southern blot hybridization
Sayhan et al.[34]	2001	Turkey	51	PCR
Soares et al.[35]	2011	Brazil	75	PCR/Dot blot
Sun et al.[36]	2013	China	75	PCR

USA: United States of America; PCR: Polymerase chain reaction; Hybridization ISH: *in situ* hybridization.

such as smoking, alcohol consumption, and obesity, combined with the elevated consumption of red meat, are also understood as risk factors. Age is also an eminent factor in the appearance of colorectal cancer, and the incidence increases significantly between the ages of 30 and 50[13].

During the clinical assessment, it is important to try to determine the stage of the disease utilizing the classification "tumor," "lymph node," and "metastasis," which allow for the planning of treatment and facilitates the study of the results of the therapy employed. The purpose of the staging of the neoplastic disease is to identify not only the locoregional extension of the primary lesion, but also its extension and distance for the decision of the best treatment option[14].

Over 180 types of HPV have already been identified, and 40 of them are related to anogenital infections. Among the HPVs with high oncogenic risk are types 16 and 18[15]. HPV 16 has been identified in up to 59.8% of invasive cancers and in over 50% of non-invasive cancers. Meanwhile, HPV 18 has been found in 15% of invasive neoplasias and in over 50% of adenocarcinomas[16].

The recurring HPV lesion is considered preneoplastic, in the form of a wart with koilocytosis, and is characterized by vegetating, non-keratotic, moist lesions, with a central nucleus of connective tissue and cauliflower-like appearance[9]. The lesion can have some malignant changes, reaching, many times, alarming proportions. Isolated or grouped, they manifest fibrous proliferations covered by pink thickened epithelial cells, without chronicity, located especially on the external genitals in the perianal area, as well as the mucous membrane[1].

For an individual to develop a disease, the presence of the specific agent in their organism is not enough[11]. Other factors, which are capable of provoking the disease along with the specific agents, need to take action. Due to HPV detection in most of the analyzed tissue with malignant tumors, there is a possible correlation with carcinogenesis in glandular cells of the colorectal mucosa[1].

Thus, the present study has the objective of assessing, systematically and through meta-analysis, the main studies that link colorectal cancer to HPV.

METHODS

The study is characterized by a systematic review with meta-analysis. The study logic employed consisted in three health databases to identify the main studies that assessed the prevalence of colorectal cancer associated with HPV.

For the diagnosis of the disease, the implementation of polymerase chain reaction (PCR) of HPV through material embedded in paraffin wax is comparable to *in situ* hybridization[4]. Thus, PCR utilizing specific initiators can detect and amplify specific portions of the HPV genome of up to 119 base pairs (BP) of HPV fragments of the types 16 and 18, which represent part of the E6 or E7 of HPV.

INCLUSION CRITERIA

To be included in the systematic review, the papers should be cross-sectional studies or a control case linking colorectal cancer to HPV. Papers without any links or reviews (narrative, systematic, or meta-analysis), case reports or guidelines were excluded.

RESEARCH STRATEGY

For the research strategy, logic based on specific descriptors was adopted (English Language) in combination with Boolean operators (AND/OR), with the aid of parentheses, to define intercalation within the same logic, and quotations marks, to identify compound words. The search was conducted in the following manner: (HPV OR "Human Papillomavirus") AND (Colorectal OR Rectal OR Colon) AND (Cancer). The databases utilized were: PubMed (Medline), ScienceDirect (Elsevier), and Scientific Electronic Library Online (SciELO) (Bireme), between April and May 2015.

To avoid the excessive inclusion of papers, the search was limited to the following fields: title, keywords, and abstract. This way, the descriptors must be contained in at least one of the three search fields (limitation filters were not added, for example: language of the paper, target audience, or date limit).

For the purpose of recruiting studies, after exporting the selected papers in the databases, a software that is specific for systematic reviews was utilized: *State of the Art through Systematic Review* (StArt)[17], which served as the base for identifying duplicate papers, both the included and excluded ones. These analyses were conducted separately by two researchers (T.P.; C.P.D.) and verified by a third editor (C.R.).

As eligibility criteria for the papers, three steps were adopted for the inclusion and exclusion: (a) papers selected by both researchers were included; (b) articles that were not selected were excluded; (c) articles included by only one researcher were analyzed by the editor, who authorized the inclusion if they fit the proposed framework.

To conduct the meta-analysis, after the eligibility of the papers and identifying the outcome variables, OpenMeta[Analyst][18] software was utilized, with randomized statistical proportion being applied (univariate), with a confidence interval of 95% (CI95%), for colorectal cancer due to HPV prevalence estimates, as well as links to HPV 16 and 18, genders (male/female), and tumor region (cervix/rectum). For the case control group, randomized statistical proportion (bivariate) was employed, with odds ratio and CI95%, for prevalence estimates for colorectal cancer due to HPV between the case control groups.

To systematically record data, the study was previously registered on the following website: *Centre for Reviews and Dissemination/International Prospective Register of Systematic Reviews* (PROSPERO) (http://www.crd.york.ac.uk/PROSPERO), under the identification number CRD42015023199.

RESULTS

Initially, 431 papers were recovered (PubMed: 325; ScienceDirect: 92; SciELO: 14) by means of electronic searches. From these, 39 were excluded due to being duplicates and 327 due to being observational studies and not fitting within the proposed framework. Thus, 65 papers were read in their entirety, with 47 being excluded because they did not meet the eligibility criteria, resulting in a total of 18 eligible papers for the systematic review (14 cross-sectional studies and four case control studies), as demonstrated in the flowchart (Figure 1).

From the 18 eligible studies[19-36], 7 (38.9%) were conducted in the United States (1), in Brazil (3), in Argentina (2), in Peru (1), 5 (27.8%) in Europe, and 6 (33.3%) in Asia.

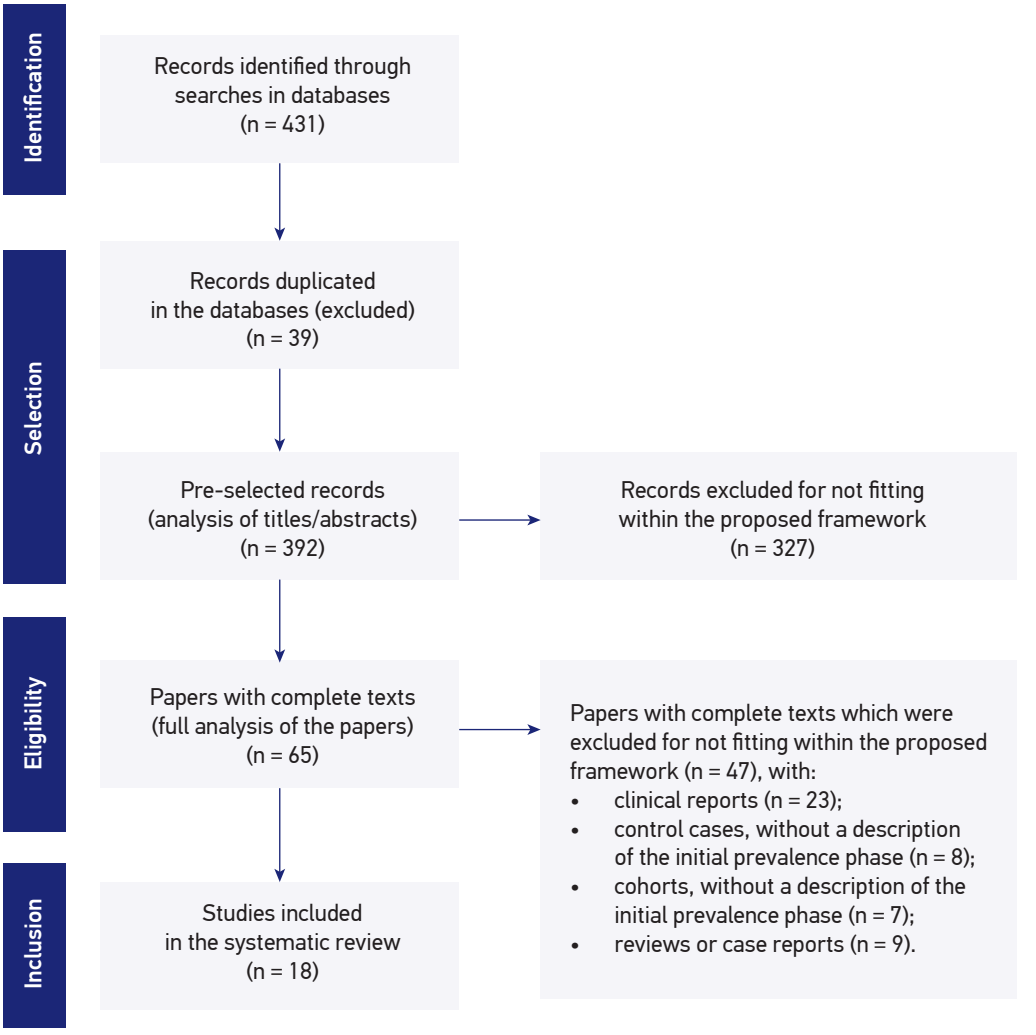


Figure 1. Flowchart of Eligible Papers.

From the 18 articles written in the last 20 years, 16 (88.9%) were published in the last 10 years (Table 1).

During this period, 1,549 samples were assessed, with 956 (61.7%) being male samples. From these, 630 cases of colorectal cancer due to HPV (51.8%) were diagnosed, of which 408 (51.9%) were males. In addition, 404 (67.5%) cases were linked to HPV 16 and 18, with tumor prevalence in the area of the cervix, 253 (61.3%), and the majority of patients were identified in stages II and III (103, 31.6%; 121, 37.8%, respectively), as exposed in Table 2.

Figure 2 presents the total prevalence of colorectal cancer due to HPV with an estimate of 51.8% (CI95% 35.7 – 66.0). When comparing cases and controls (98/262; 28/224, respectively), in 4 of the 18 studies[22,30,32,35], the estimate of the difference of colorectal cancer risk due to HPV was 24.3% (CI95% 4.5 – 44.0), with odds ratio values of 4.661 (CI95% 2.500 – 8.688) (Figure 2).

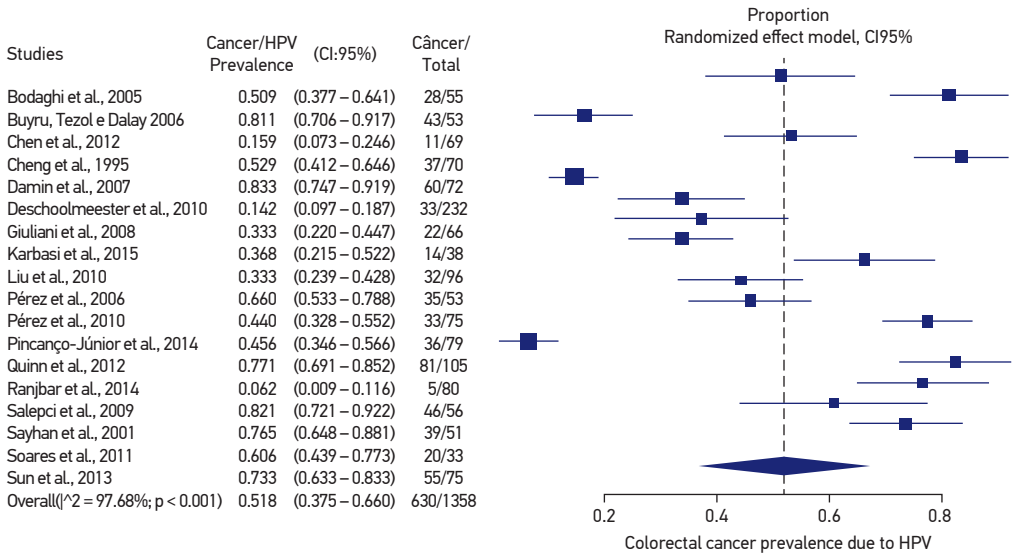
When comparing genders, 10 out of the 18 eligible papers were assessed, from the total of 767 samples, for the estimate of colorectal cancer prevalence, indicating similar values for males and females, 408 (51.9%; CI95% 46.5 – 57.3) and 359 (48.1%; CI95% 42.7 – 53.5), respectively.

Meanwhile, for the estimate of prevalence due to HPV 16 and 18, 16 of the 18 eligible papers were assessed (Figure 3), from the total of 598 samples, presenting very similar

Table 2. Analysis of the means and frequencies extracted from the studies.

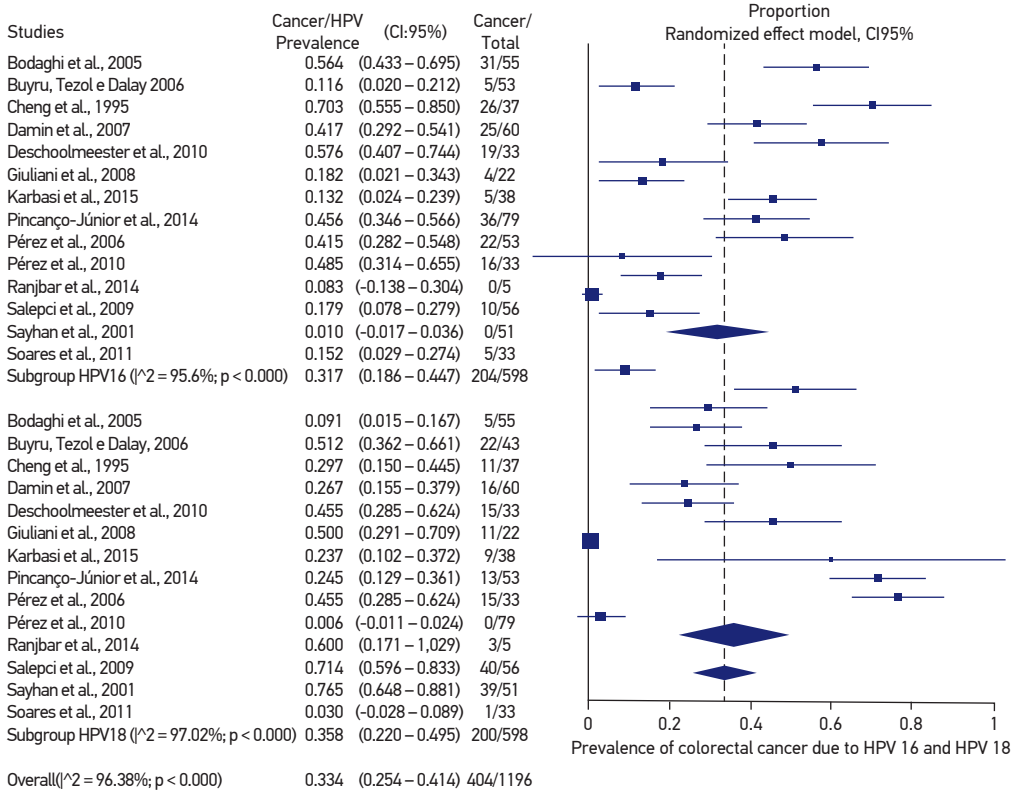
	n	%	Mean ± SD
Time of publication(1995 a 2015)			2009 ± 5.0
Age (18 to 88 years old)			53.9 ± 10.5
Sex (male)	956/1,549	61.7	
Cancer/HPV	630/1,358	51.8	
Cancer/HPV (male)	408/767	51.9	
Câncer/HPV 16	204/598	31.7	
Cancer/HPV 18	200/598	35.8	
Area of cancer/HPV			
Cervix	253/411	61.3	
Rectum	158/411	38.7	
Stage of cancer/HPV			
I	52/320	162	
II	101/320	31.6	
III	121/320	37.8	
IV	46/320	14.4	

SD: standard deviation; HPV: human papillomavirus.



CI95%: Confidence interval of 95%; HPV: human papillomavirus.

Figure 2. Estimate of colorectal cancer prevalence due to human papillomavirus.



CI95%: Confidence interval of 95%; HPV: human papillomavirus.

Figure 3. Estimate of colorectal cancer due to human papillomavirus 16 and 18.

numbers for the types of manifestation of the virus, 204 (31.7%; CI95% 18.6 – 44.7) and 200 (35.8%; CI95% 22.0 – 49.5), in this order.

In the assessment of the estimate of colorectal cancer prevalence by region, eight of the 18 papers[21,23-26,29,30,32], from the total of 411 samples, presented relatively expressive values for the cervical area, 253 (61.3%; CI95% 50.4 – 72.3) and for the rectal area, 158 (38.7%; CI95% 27.7 – 49.6).

DISCUSSION

After analyzing the published manuscripts from the last two decades, it became evident that there is a link between colorectal cancer and HPV. Expressive values were observed in the prevalence of HPV (51.8%) (Figure 2), especially for types 16 and 18 (Table 2 and Figure 3), due to late diagnosis, seeing that the confirmation of the disease is more frequent in stage III (Table 2). Another factor that was observed is the lack of evidence in the differences between genders regarding the prevalence of colorectal cancer due to HPV, seeing that both sexes presented similar values.

Based on the complete reading of the 18 eligible papers for the systematic study[19-36], it was found that the location where HPV is most predominant is the cervical area, the vulva, the vagina, and the anus, since they are associated with chronic infections, preceded by non-malignant precursor lesions, like the cervical squamous intraepithelial lesion (CSIL) and the anal squamous intraepithelial lesions (ASIL), with predilection being shown for the zone of cellular transition of glandular squamous cells, seeing that both have common biological characteristics, including histopathological aspects.

In the assessed studies, the samples from the patients diagnosed with colorectal carcinomas pointed to one or more copies of viral HPV DNA, since viral HPV presents tropism through glandular epithelial cells and is the cause of skin and mucosal infections. According to Giuliani et al.[25], taking into consideration the known molecular mechanisms of these individual viruses, there is a possibility that they will alter the control mechanisms of the cellular cycle, inhibiting apoptosis, causing chromosomal instability, and promoting colorectal oncogenesis.

Bodaghi et al.[19], Damin et al.[23], and Sun et al.[36] affirm that, although the number of HPV DNA copies may be low, viral HPV plays an active role in the pathogenesis of the colorectal carcinoma, displaying higher prevalence of type 16, followed by type 18. Thus, it is possible to affirm that, overall, the viral cause favors genetic instability and contributes to carcinogenesis.

The dot blot hybridization has been utilized in various studies with the intention of detecting HPV DNA in material extracted through biopsies. This method presents lower sensibility and specificity when compared to the Southern blot hybridization. This data can

explain the variation noted worldwide regarding the prevalence of HPV in the most varied areas of the human body, due to the techniques employed to detect HPV DNA (Table 1).

It is a well-established fact that the accumulation of genetic alterations can lead to the development of cancer. This phenomenon has been extensively investigated by various authors, above all regarding colorectal cancer, whose model is considered ideal for the comprehension of the carcinogenic process, due to the progression from pre-malignancy to malignancy. However, Picanço-Júnior et al.[30] did not find a correlation between staging and cellular differentiation with the presence of HPV 16, despite being evident in other systematic studies that HPV infection can be a risk factor for the increase of colorectal cancer prevalence. It is possible that the discrepancy in the results found by Picanço-Júnior et al.[30] is linked to the use of different techniques or inadequate material, which causes the lack of evidence in these studies.

CONCLUSION

During the research period of this study, colorectal cancer owing to HPV was diagnosed in 51.8% of cases. Of these, the majority was linked to HPV 16 and 18, with tumor prevalence in the cervical area and a similarity between genders. Therefore, HPV infection, as nowadays it is one of the most common sexually transmitted diseases worldwide and as it is linked to colorectal cancer, has become an important method in early diagnosis for the prevention of new cases, and it also enables new studies to facilitate the prognostic and treatment of the disease.

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