

## REVIEW ARTICLE

**HPV infection as a risk factor of esophagus squamous cell carcinoma and its prognosis***A infecção do HPV como fator de risco para o carcinoma de células escamosas de esôfago e seu prognóstico*

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**ABSTRACT:** Esophageal cancer is the 8th most common cancer in the world, with a survival rate of around 20% in five years. The most common histological type is squamous cell carcinoma, which presents geographical and ethnic variations. The risk factors for this pathology are not well defined. One of the main ones is infection by the Human Papilloma Virus (HPV), which presents frequent but transient conditions, which may regress spontaneously. The subtypes with the highest risk of malignancy are 16 and 18. Thus, a systematic review of the literature was performed based on the reference data, such as Medline, The Cochrane Library, Embase and Lilacs. Articles in languages other than English, Portuguese and Spanish; articles where the full recovery was not possible; those that had missing or insufficient data for evaluation the variables under study; those that focused on the pediatric population, animals and/or cell lines; presence of HPV in extra-esophageal locations; benign lesions or malignant neoplasms other than squamous cell carcinoma (SCC); and case reports or case series were excluded. The study analyzed 64 abstracts of articles, 25 of which were included in this review and 39 excluded. The study demonstrated the presence of HPV in the esophageal SCC in 648 (24.4%) of the 2647 neoplastic tissue samples, detected by different techniques. We observed, however, that this great prevalence is very related to the geographic region studied. Finally, it was considered that in fact there is a relationship between HPV and esophageal SCC, as analyzed in the vast majority of studies, but it is not yet possible to reach an effective conclusion about its interference in the patient's prognosis.

**Keywords:** HPV infections; Human Papillomavirus infection; Esophagus cancer; Esophageal neoplasm; Prognostic

**RESUMO:** O câncer de esôfago é o 8º mais comum no mundo, com uma taxa de sobrevivência em torno de 20% em cinco anos. O tipo histológico mais frequente é o carcinoma de células escamosas, o qual apresenta variações geográficas e étnicas. Os fatores de riscos para tal patologia não são bem definidos. Um dos principais é a infecção pelo Papiloma Vírus Humano (HPV), que apresenta quadros frequentes, porém transitórios, podendo regredir espontaneamente. Os subtipos que apresentam maior risco de malignidade são o 16 e 18. Dessa forma, uma revisão sistemática da literatura foi realizada a partir da base de dados de referência, como Medline, The Cochrane Library, Embase, Lilacs. Foram aplicados os critérios de exclusão e inclusão e assim obteve o resultado e assim 25 artigos incluídos nessa revisão e 39 excluídos. O estudo demonstrou presença do HPV no CEC de esôfago em 648 (24,4%) das 2647 amostras de tecidos neoplásicos, detectados através de diferentes técnicas. O que foi observado, todavia, é que essa grande prevalência muito se relaciona à região geográfica estudada. Por fim, foi considerado que de fato existe uma relação entre o HPV e o CEC de esôfago, como analisado na grande maioria dos estudos, porém ainda não se pode chegar a uma conclusão efetiva acerca da sua interferência no prognóstico do paciente.

**Descritores:** Infecção por HPV; Infecção por Papilomavírus Humano; Câncer de esôfago; Neoplasia de esôfago; Prognóstico.

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## INTRODUCTION

Esophageal cancer is the eighth most common cause of cancer and the sixth most common cancer-related death<sup>1</sup>. In Brazil, excluding non-melanoma skin cancer, it is the sixth most incident among men and thirteenth among women<sup>2</sup>. Its prognosis is poor, with a survival rate of around 20% over five years. The most common histological type in the world is still squamous cell carcinoma, with geographical and ethnic variations, followed by adenocarcinoma<sup>1</sup>. The risk factors for the development of esophageal squamous cell carcinoma are not well defined, with the use of alcohol and tobacco accountable as the main etiological factors. Infection with the human papilloma virus (HPV) has been reported as a risk factor for this neoplasm<sup>1</sup>. HPVs are viruses capable of infecting the skin or mucous membranes. The infection is very frequent but transient, spontaneously regressing most of the time. In the minority of cases, the infection may persist and develop precursor lesions which, if not identified and treated, can progress to cancer, especially in the cervix, but also in the vagina, vulva, anus, penis, oropharynx and mouth, and the subtypes 16 and 18 are responsible for 80% of the cases of malignancy<sup>1</sup>.

## OBJETIVE

The aim of the study is to perform a systematic review of the literature in order to establish the correlation between esophageal squamous cell carcinoma and HPV infection, as its risk factor and to evaluate its prognosis in relation to lesions not linked to the virus.

## MATERIALS AND METHODS

### Ethical aspects

The present study was not submitted to the Ethics Council of the Institution involved because it is a systematic review, presenting only articles already published.

### Search strategy, inclusion and exclusion criteria

Three authors searched the following electronic database: Medline, The Cochrane Library, Embase and Lilacs (Latin American and Caribbean Health Sciences). The search involved articles in Portuguese, English and Spanish, published until 2018, with a broad search strategy to avoid publication bias. The following keywords were used: "squamous-cell carcinoma", "esophagus cancer", "human papillomavirus", "HPV", "squamous cell carcinoma" and "esophageal cancer".

Articles in languages other than those mentioned above were excluded, or those that concluded that full recovery was not possible. Those studies that did not

contain data or insufficient data to evaluate the variables under study were also excluded. Articles that focused on the pediatric population, animals, cell lines, the presence of HPV in extra-esophageal locations, benign lesions or malignant neoplasms other than squamous cell carcinoma (SCC), case reports or case series were also excluded. Systematic review articles were used to discuss the results, not being used as part of these.

### Data extraction

The data were extracted by two independent authors. For this, a data registration form was used for this purpose, including: type of study, country of origin, time of sample collection, number of patients with esophageal SCC, numbers of patients in the control groups, harmful habits (smoking and drinking), technology used in the study for the detection of HPV (polymerase chain reaction - PCR, *in situ* hybridization and/or immunohistochemistry - IHC), number of patients affected by HPV, identification of HPV type (HPV16 and/or HPV18) and 5-year survival.

### Data analysis

Initially, to facilitate the analysis, the articles were organized in the following groups: (1) oral or oropharyngeal HPV infection in patients with esophageal SCC; (2) Esophageal SCC and correlation with HPV; (3) Harmful habits and patients with esophageal SCC/HPV positive; (4) Overall 5-year survival of positive and negative HPV esophageal SCC patients.

We used the Microsoft Excel software (Microsoft Corp. (r), Redmond, WA) to tabulation of data and calculations of the weighted average, frequency and 95% confidence interval (95% CI). The SPSS (r) version 17.0 (SPSS (r) Inc.; Illinois, USA) software for regressions was used to assess the risk of HPV infection in each group, with calculation of odds ratios (OR) and 95% CIs. In all of these analyzes, the likelihood of occurrence of a  $\alpha$  or type I error was considered to be less than 5% ( $p < 0.05$ ).

## RESULTS

The study analyzed 64 abstracts of articles, excluding articles approaching only about HPV molecular biology; unrelated to the subject (28); benign neoplasms or only the HPV infection in the esophagus (15); studies that did not specify the type of malignant neoplasm or those including malignant neoplasms from other HPV-associated topographies; making it impossible to calculate the variables in question (12) and systematic reviews (13); as shown in the flowchart in Figure 1.

Based on these criteria, 25 articles were included in the review, with results obtained according to Tables 1, 2, 3, and 4 and in Figures 2 and 3.

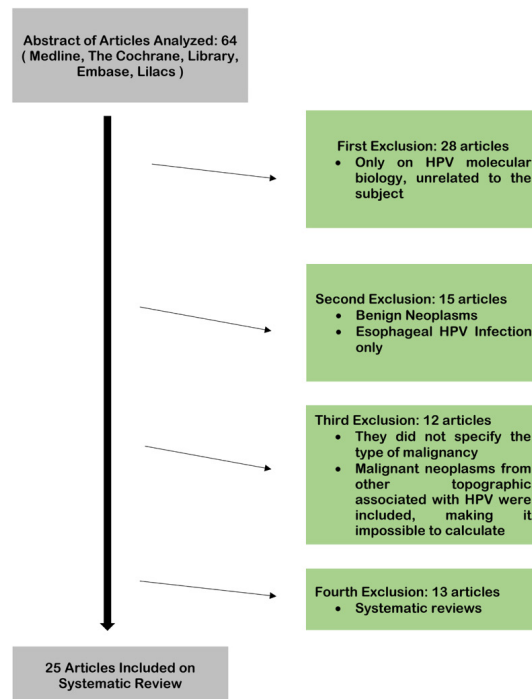


Figure 1: Flowchart of articles

Table 1. Demographic data of patients and sample of studies included in the review

Article	Country	Average age	Men / Womens	Smoking (n/HPV+)	Alcohol (n/HPV+)
Cao 2014 <sup>4</sup>	China	60 (42-78)	84/21	63/14	52/15
Dreilich 2006 <sup>5</sup>	Suécia	> 65	71/29	67/10	50/6
Fuhirata 1993 <sup>6</sup>	Japão	60-70	62/9	∅	∅
Kumar 2015 <sup>7</sup>	Índia	>45	67/34	53/11	
Souto-Damin 2016 <sup>8</sup>	Brasil	58,4 (45-85)	105/50	∅	∅
Wang 2015 <sup>9</sup>	China	49,9 (40-66)	147/3	144/27	147/26
Mehyar 2015 <sup>10</sup>	China	∅	∅	∅	∅
Turkay 2016 <sup>11</sup>	Turquia	>70	18/15	∅	∅
Soheli F 2016 <sup>12</sup>	Irã	62,63	70/33	∅	∅
Prokash 2017 <sup>13</sup>	Índia	60 (42-70)	9/9	10/5	5/2
Costa 2017 <sup>14</sup>	Brasil	60,9 (41-92)	100/23	99/10	97/10
Bahmassy 2005 <sup>15</sup>	Egito	61,3 (40-72)	34/16	∅	∅
Zhang 2017 <sup>16</sup>	China	62 (44-76)	155/37	62/40	59/38
Geßner 2010 <sup>17</sup>	Malawi	60	27/13	∅	∅
Haeri 2013 <sup>18</sup>	Irã	59,6 (30-83)	16/14	∅	∅
Fahradi 2005 <sup>19</sup>	Irã	54 (25-75)	38/38	∅	∅
Antonsson 2010 <sup>20</sup>	Austrália	65,2	140/127	188/75	94/41
Guo 2012 <sup>21</sup>	China	51-60	712/488	519/∅	203/∅
Benamouzig 1992 <sup>22</sup>	França	∅	∅	∅	∅
Talamini 2000 <sup>23</sup>	Itália	>57	41/4	36/29	41/29
Haohua 2014 <sup>24</sup>	China	63	144/33	∅	∅
Hayedeh 2013 <sup>25</sup>	Irã	62 (41-82)	14/16	∅	∅
Herbster 2012 <sup>26</sup>	Brasil	60,31	184/52	211/24	199/18
Andrzej 2012 <sup>27</sup>	Polônia	59	49/7	∅	∅
Herrera-Goepfert 2009 <sup>28</sup>	México	61 (27-85)	47/13	28/6	36/9

∅ : data not available in the article

**Table 2.** Prevalence of HPV in esophageal squamous of cells carcinoma samples from studies included in the review

Article	Study time (Years)	N (CEC)	HPV positive cases / (%)
Cao 2014 <sup>4</sup>	02	105	29 (27,6)
Dreilichi 2006 <sup>5</sup>	10	100	16 (16)
Fuhirata 1993 <sup>6</sup>	11	71	24(33,8)
Kumar 2015 <sup>7</sup>	04	101	22 (22)
Souto-Damin 2006 <sup>8</sup>	07	165	26 (15,7)
Wang 2015 <sup>9</sup>	03	150	27 (18)
Mehyar 2015 <sup>10</sup>	02	198	158 (79,7)
Turkay 2016 <sup>11</sup>	13	33	3 (9,09)
Soheili F 2016 <sup>12</sup>	06	103	11 (10,7)
Prakash 2017 <sup>13</sup>	01	18	09 (50)
Costa 2017 <sup>14</sup>	01	87	12(13,8)
Bahrnassy 2005 <sup>15</sup>	02	50	27 (54)
Zhang 2017 <sup>16</sup>	03	192	67 (34,9)
Geßner 2010 <sup>17</sup>	/	40	6 (15)
Haeri 2013 <sup>18</sup>	02	130	0 (0)
Fahradi 2005 <sup>19</sup>	05	38	14 (36,8)
Antonsson 2010 <sup>20</sup>	03	222	8 (3,5)
Guo 2012 <sup>21</sup>	01	300	99 (33)
Benamouzig 1992 <sup>22</sup>	/	12	5 (41,6)
Talamini 2000 <sup>23</sup>	08	45	2 (4,4)
Haohua 2014 <sup>24</sup>	12	177	6 (3,3)
Hayedeh 2013 <sup>25</sup>	02	30	0 (0)
Herbster 2012 <sup>26</sup>	09	264	34 (13)
Andrzej 2012 <sup>27</sup>	03	56	28 (50)
Herrera-Goepfert 2009 <sup>28</sup>	08	60	15 (25)
<b>Total</b>		<b>2647</b>	<b>648 (24,4; IC95 16,6 - 32,3)</b>

**Table 3.** 5-year survival of patients with esophageal SCC according to studies included in the review.

Article	5 year survival (HPV +/- %)
Cao 2014 <sup>4</sup>	65,5 / 43,4
Dreilich 2006 <sup>5</sup>	11,0 / 11,0
Fuhirata 1993 <sup>6</sup>	9,2 / 22,8
Kumar 2015 <sup>7</sup>	72,2 / 49,3
Antonsson 2010 <sup>20</sup>	75 / 36
Herbster 2012 <sup>26</sup>	0 / 0
Wang 2015 <sup>9</sup>	48 / 21
5 years survival	HPV+ 35,9% (IC95: 19,9 - 51,9) HPV- 21,9% (IC95: 8,7 - 35,1)

**Table 4.** HPV as a risk factor of esophageal SCC in the studies included in the review

Article	HPV +	HPV -	SCC	Control
Geßner 2010 <sup>17</sup>	7	47	40	15
Haeri 2013 <sup>18</sup>	0	0	30	30
Fahradi 2005 <sup>19</sup>	19	59	40	38
Antonsson 2010 <sup>20</sup>	8	269	222	55
Guo 2012 <sup>21</sup>	154	1046	300	900
Benamouzig 1992 <sup>22</sup>	6	17	15	8
Andrzej 2012 <sup>23</sup>	32	59	56	35
Total (p≤0,05)	226	1558	702	1081

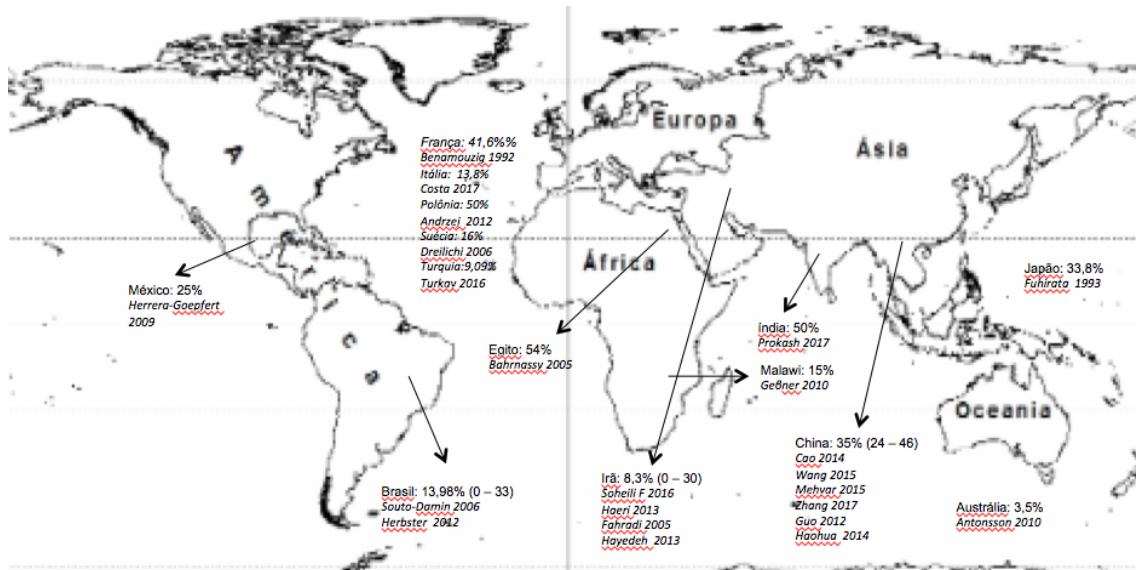


Figure 2. Articles according to the countries of publication.

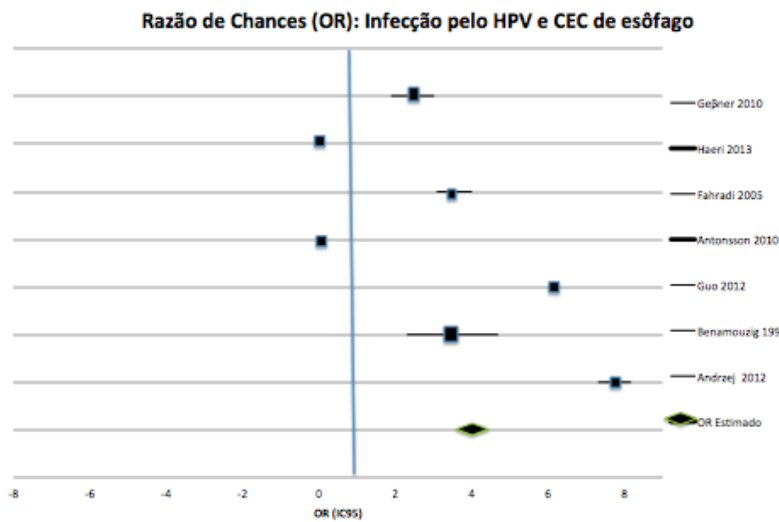


Figure 3. Forest-plot OR.

## DISCUSSION

Esophageal carcinoma can already appear as a frankly malignant lesion or appear as a progression of premalignant lesions. The tumor begins in the internal lining

layer of the organ (mucosa), penetrating the submucosa, muscular layer and adventitia, and may infiltrate adjacent organs, such as the trachea or the aorta.

Its etiology is associated with the histological type of the disease, and the squamous cell carcinoma is still

the most common and strongly related to smoking and alcohol consumption, and adenocarcinoma, associated with Barrett's esophagus and obesity. Among other factors described, consumption of food and water rich in nitrates and nitrosamines, low intake of fruits and vegetables, mycotoxins, consumption of high temperature drinks, palmoplantar tylosis, Plummer-Vinson syndrome, achalasia, caustic strictures and genetic factors are also related to this type of cancer.

HPV has been implicated as a risk factor for esophageal squamous cell carcinoma since 1982, by the study by Syrjänen et al.<sup>29</sup>, describing the progression of the lesion from flat condyloma to invasive carcinoma. Among the 100 types of HPV, the 16 and 18 are those with the highest rates of oncogenic predisposition. They are attracted to squamous epithelial cells on wet surfaces, including the mucosa of the genital and aerodigestive tracts, in addition to the skin, and can remain throughout their life cycle, including replication<sup>28</sup>.

The study by Patham et al.<sup>30</sup> in 2017 analyzed the presence of esophageal papilloma and HPV through PCR in patients undergoing upper digestive endoscopy in 13 years, with 60 cases of papilloma found in this period, and of these, 19 paraffinized tissues remaining from incisional biopsy of the lesion performed in the procedure underwent DNA virus research 9 had positive PCR for HPV 16. (47.4%)<sup>27</sup>.

Our study showed the presence of HPV in the esophageal SCC in 648 (24.4%) of the 2647 samples (Table 2) of neoplastic tissues, detected using different techniques. This prevalence varies widely according to location, with higher incidences presented in Chinese studies, in which the prevalence of the virus in cases of esophageal SCC was around 35%. The meta-analysis by Ludmir et al.<sup>31</sup>, showed the same geographical difference, especially when the patients involved were from Asia, in which the percentage of HPV in the esophageal SCC reached 38%, in contrast to studies involving patients from South America, in which the study with the highest prevalence was 16.6%<sup>21</sup>. The systematic review performed by Zhang et al.<sup>32</sup> in 2014, analyzed 26 studies with a total of 3026 patients with esophageal SCC from all regions of China, assessing the presence of HPV 16 in neoplastic tissues. A prevalence of 39.7% was demonstrated, with a greater predominance in the southern region of the country, which had a prevalence of 47.8%, despite presenting the lowest number of cases

studied than in other regions<sup>21</sup>.

The 2015 meta-analysis by Guo et al.<sup>33</sup>, also performed in China, researched the presence HPV 18 in patients with esophageal SCC, involving 2556 patients, showing that this subtype was present in 4.1% of the lesions<sup>33</sup>.

In contrast, the 2013 systematic review by Li et al.<sup>34</sup>, analyzed the remaining histological analysis of 8990 cases of esophageal SCC, which underwent PCR, with prevalence of 22.2% of virus DNA, with a predominance of HPV 16<sup>34</sup>. The importance of high prevalence of HPV infection in China is found in the country's large population, associated with the flow of emigration and transit of its citizens around the world after its economic expansion.

The articles evaluated in our study suggest a strong association between HPV and esophageal malignancy in question, in view of the prevalence of the virus in the studies and the OR calculated from 7 present case-control articles was 3.93 (CI: 95, 3.83-4.02). It must be remembered that, as shown in table 1, patients infected with HPV also have a history of smoking and drinking habits, which can be a confusing factor for establishes it as a risk factor. The systematic review by Li et al.<sup>34</sup> had as a result of its OR 3.32 (CI: 95, 2.26-4.87) in 17 evaluated articles.<sup>34</sup> The 2013 Syrjänen<sup>29</sup> meta-analysis, involving 39 studies to verify the difference between the virus detection methods, demonstrated that the presence of the virus cannot really be associated with the etiology of lesion<sup>29</sup>.

The meta-analysis by Guo et al.<sup>35</sup>, 2016, involved 1184 cases of esophageal SCC, analyzing the risk of death in positive and negative HPV patients, demonstrating that the presence of the virus (0.73 relative risk, CI:95, 0.44-1.21) has no interference in the prognosis of the neoplasia<sup>35</sup>. The articles in which the overall 5-year survival analysis (Table 3) was present, there was no difference between patients infected by the virus and those not infected.

## CONCLUSION

The studies evaluated by systematic review and meta-analysis show that there is an association between HPV and esophageal cancer, especially in certain geographic areas, without having greater influences on the patient's prognosis. More studies, essentially prospective cohort studies should be performed to detail its role in the oncogenesis of esophageal SCC and thus, establish it definitively as a risk factor and thus, build prevention strategies.

**Authors' participation:** *Gilberto Mendes Menderico Júnior*: Prof. Dr. project advisor and supervisor. *Nathalie Gabrielle Gomes Lessa Altieri*: Academic of medical school, that participated in the planning, design, critical intellectual review, data analysis and preparation of the manuscript until final approval for publication. *Leticia Pacolla Izique*: Academic of medical school, that participated in the planning, design, critical intellectual review, data analysis and preparation of the manuscript until final approval for publication. *Ana Carolina Ferrari Nassar*: Academic of medical school, that participated in the planning, design, critical intellectual review, data analysis and preparation of the manuscript until final approval for publication. *Julia Royd Costa Salvio*: Academic of medical school, that participated in the planning, design, critical intellectual review, data analysis and preparation of the manuscript until final approval for publication. *Débora de Oliveira Garcia*: Academic of medical school, that participated in the planning, design, critical intellectual review, data analysis and preparation of the manuscript until final approval for publication. *Carolina Isper*: Academic of medical school, that participated in the planning, design, critical intellectual review, data analysis and preparation of the manuscript until final approval for publication.

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