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The relationship between esophageal cancer, chagasic megaesophagus and HPV: myths, tales or reality?

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Running title: Esophageal cancer: Chagas' disease and HPV

Abstract

A supposed role for persistent high-risk human papillomavirus (HPV) infection in esophageal squamous cell carcinoma (ESCC) etiology has been suggested by a number of studies. Concomitantly, megaesophagus induced by the Trypanosoma cruzi cell-cycle activity also shows a potential association with ESCC. This review discusses esophageal cancer and the potential association between chagasic megaesophagus and HPV as risk factors for ESCC development.

Keywords: Epidemiology, Chagas disease, *Trypanosoma cruzi*, megaesophagus, esophageal cancer, squamous cell carcinoma, human papillomavirus; HPV.

Background

Esophageal cancer (EC) is a very aggressive tumor with high incidence and mortality worldwide. Approximately 500,000 new cases are diagnosed each year with around 406,000 deaths per year (Globocan, 2012). In Brazil, 2,860 cases are estimated for women and 7,950 for men in 2016 (INCA, 2016). The megaesophagus, caused by Chagas' disease, is one of several risk factors for EC development. Another potential risk factor associated to this disease is the persistent infection of *human papillomavirus* (HPV); however, the association between HPV and megaesophagus is tentative and has been scarcely reviewed in the literature (Crema *et al.*, 2010). This review aims at emphasizing the importance of esophageal cancer and better discuss the association of two of its risk factors: chagasic megaesophagus and HPV.

Chagasic disease

The American *trypanosomiasis*, also known as Chagas' disease (CD), is a tropical parasitic disease caused by the protozoan *Trypanosoma cruzi* and is associated to the microenvironment, social and economic changes (Dias and Macedo, 2005). The highest occurrences are in South and Central America countries and Mexico (Machado *et al.*, 2012), with approximately 10 million infected people, being considered a critical public health problem (Machado *et al.*, 2012). However, non-endemic regions such as Canada, Europe, Australia, Japan, Spain, Portugal and United States may present some cases of the disease due to migration of infected individuals from Latin American (Aufderheide *et al.*, 2004, Machado *et al.*, 2012).

The disease transmission can occur by vector, transfusion (blood and organs), vertical transmission (from mother to child) or contaminated food ingestion (Bonney, 2014). The vector transmission to the human host occurs through the deposition of insect faeces containing the protozoon *Trypanosoma cruzi* while biting the host dermis (Giddings *et al.*, 2006, Gutierrez *et al.*, 2009, Rassi *et al.*, 2010, Nagajyothi *et al.*, 2012). When the faeces reach the human bloodstream, the vector lifecycle begins (Giddings *et al.*, 2006, Gutierrez *et al.*, 2009, Rassi *et al.*, 2010, Nagajyothi *et al.*, 2012) (Figure 1).

Figure 1. Life cycle of *Trypanosoma cruzi* showing the various forms of the protozoan. Adapted from the Centers for Disease Control and Prevention **(Prevention, 2015)**.

Chagas' disease can be classified into two phases: acute and chronic (Kowalska *et al.*, 2011); approximately 30% of infected individuals develop the chronic form

(Kowalska *et al.*, 2011). In general, the acute or initial phase lasts 4 to 8 weeks, whilst chronic or indeterminate disease may last for 10-30 years (Nunes D. P MAL *et al.*, 2004). The clinical manifestations between both phases also differ one from another, being discreet or undetectable in acute phase (Nunes D. P MAL *et al.*, 2004). Normally, the acute symptoms include inflammation at the site of inoculation ("chagoma" inoculation), hepatosplenomegaly or lymphadenopathy, palpebral edema (Pomegranate signal), enlarged lymph nodes and splenomegaly (Rassi *et al.*, 2010, Bonney, 2014). And, in the chronic phase, it can be detected in the heart, gastrointestinal organ, cardiodigestive or a mixed form of concomitant sites. The anatomical physiognomy changes to megacolon, megaesophagus and cardiomegaly and positive serological tests (Nunes D. P MAL *et al.*, 2004).

Chagasic Megaesophagus

The understanding of Chagas' disease is important due to its occurrence not being restricted to endemic areas (Souza *et al.*, 1904), and since the chronic disease can cause the destruction of the enteric system in humans (Oliveira *et al.*, 1998).

Pathophysiology

The Chagasic megaesophagus (CM) is one of the clinical manifestations of Chagas chronic disease. It is caused by the destruction of the myenteric plexus (plexus of Auerbach – parasympathetic) (Bellini *et al.*, 2012, Gullo *et al.*, 2012, Souza *et al.*, 2013) of the esophagus that coordinates motor activity of the esophagus to the rectum, in response to local inflammation and immune mechanisms (Bellini *et al.*, 2012, Souza *et al.*, 2013). The destruction caused by direct parasitism of the nerve cell (action of neurotoxins, inflammatory action and autoimmune mechanism) leads to achalasia. The neurons are in varying degrees of destruction, and there is neuritis, perineuritis and ganglionitis (Adad *et al.*, 1991) (Figure 2).

Figure 2. Photomicrographs cases of megaesophagus and esophagus without megaesophagus. Adapted from Côbo *et al (Cobo Ede et al., 2012).*

The mesenteric ganglionitis node is due to a crusade immunoreactivity flagellar antigen caused by the parasite that mimics a protein expressed by intestinal neurons, which attracts immune cells into the lymph nodes, leading to the disappearance and its replacement by dense connective tissue, and interstitial fibrosis between muscle fibers

(Ribeiro-dos-Santos R *et al.*, 1976, Adad *et al.*, 1991). The enteric nervous system (ENS) is important in gastrointestinal disorders due to CD (Bellini *et al.*, 2012, Souza *et al.*, 2013). The mucosal hyperplasia and muscle hypertrophy caused by plexus degeneration or intrinsic parasympathetic postganglionic denervation (Bellini *et al.*, 2012, Souza *et al.*, 2013). The *Trypanosoma cruzi* causes tissue injury through direct action in target cells and indirectly through the induction of hypersensitivity (Hoffman and Schnitzlein, 1961, Gullo *et al.*, 2012).

The CM occurs due to achalasia of the lower sphincter (ALS), which is the destruction of the intramural nerve plexus leading to the absence of peristalsis and no harmonic opening of the lower esophageal sphincter a due to deglutition, causing food retention, chronic esophagitis and acanthosis; these persistent conditions may lead to precancerous lesions. The individuals affected often have difficulty swallowing liquids and solids, have regurgitation and heartburn, including chest pain, coughing and weight loss, and respiratory complaints that occur less frequently (Kraichely and Farrugia, 2006, Mabvuure *et al.*, 2014). Additionally, individuals with CM have a wide variety of esophageal microbiota, consisting of anaerobic Gram-positive bacteria that are related to the degree of esophageal dilatation. The untreated achalasia leads to the progressive increase of the esophagus (megaesophagus) (Pajecki *et al.*, 2002, Gockel *et al.*, 2006, Mabvuure *et al.*, 2014).

Chagasic megaesophagus and esophageal cancer

Advanced megaesophagus can increase the probability of developing esophageal squamous cell carcinoma (ESCC) by 3 to 8% when compared to the general population (Adad *et al.*, 1991). This cancer occurs due to prolonged contact with food in the esophageal mucosa, also increasing bacterial growth, chemical irritation, resulting in a chronic esophagitis (Safatle-Ribeiro *et al.*, 2000, Brucher *et al.*, 2001, Pajecki *et al.*, 2002, Gockel *et al.*, 2006, Gullo *et al.*, 2012, Tustumi *et al.*, 2017). Carcinogenesis can be related to the production of nitrates and mediated by bacteria, which are present in liquid stasis and have mutagenic potential in the cellular DNA. The appearance of bacteria is another factor, which involves the appearance of epithelial dysplasia and esophageal cancer (Pajecki *et al.*, 2003, Gullo *et al.*, 2012).

Brandalise and cols. analyzed 140 patients with megaesophagus and found that 9.2% of them developed esophageal cancer (Brandalise *et al.*, 1985). A study by Pinotti and cols. reported the occurrence of 12 cases of esophageal cancer (3.9%) in 308 patients

with megaesophagus (Pinotti *et al.*, 1980). The *Trypanosoma cruzi* infection is not sufficient to increase the occurrence of esophageal cancer in patients with CD without megaesophagus (Gullo *et al.*, 2012). However, individuals with megaesophagus have the same risk of developing cancer as individuals with idiopathic achalasia, suggesting that esophageal cancer is related to achalasia and megaesophagus instead of CD (Gullo *et al.*, 2012).

Individuals with chagasic megaesophagus with or without esophageal carcinomas, show changes in expression of p53, p16 and MIB1 (Bellini *et al.*, 2012). Studies suggested that changes in *TP53* in achalasia epithelium could be considered a biomarker to identify individuals at higher risk of developing ESCC (Bektas *et al.*, 2001, Lehman *et al.*, 2001). Other studies, using immunohistochemistry, strengthened the importance of p53 expression as a biomarker for precursor lesions, showing the high frequency of p53 protein with increased expression in megaesophagus when compared to normal individuals (Bektas *et al.*, 2001, Lehman *et al.*, 2001, Bellini *et al.*, 2008).

A study from our group (Lacerda *et al.*, 2017) described for the first time mutations in *TP53* gene in patients with esophageal cancer associated with chagasic megaesophagus, and a high frequency of mutation found (13/32, 40.6%) suggested that this gene also plays an important role in carcinogenesis in this pathological condition.

In addition, another important point is that according to some studies, HPV infection in patients with esophageal cancer who present mutation of the *TP53* gene have better prognosis and response to treatment (Zhang *et al.*, 2017). However, in relation to patients with chagasic megaesophagus with esophageal cancer, there are still no studies investigating the presence of HPV with mutation status of the *TP53* gene and response to treatments.

Cancer identification in patients with megaesophagus is difficult because the symptoms are hampered and frequently totally masked by severe dysphasia caused by the disease. The diagnosis is consequently delayed, mainly when the individual is in advanced stage leading to a poor prognosis (Bellini *et al.*, 2010).

Few studies have addressed the genetic changes concurrent with megaesophagus; genetic alterations associated with cell cycle regulation similar to those that occur in esophageal carcinoma have been suggested consistent with a role for megaesophagus in the development of esophageal carcinogenesis (Bellini *et al.*, 2012).

Esophageal cancer

Epidemiology

Approximately 500 thousand new cancer cases of cancers are diagnosed annually and account for more than 400 thousand deaths annually, with the vast majority of them occurring in developing countries (Globocan, 2012, Zhang *et al.*, 2015). Esophageal cancer (EC) is reported as the eighth most common cancer in both genders and the sixth leading cause of death worldwide (Globocan, 2012). A greater incidence of esophageal cancer has been reported, since 1960, in northern Iran to north-central China, considering this region as the "esophageal cancer belt" (Mahboubi *et al.*, 1973, Ferlay *et al.*, 2008, Gholipour *et al.*, 2008, Roshandel *et al.*, 2014, Xu *et al.*, 2015, Zhang *et al.*, 2015) while Brazil, Chile and South African countries are also considered high risk areas (Lopes and Fagundes, 2012, Zhang *et al.*, 2015). The prognosis and diagnosis are unprofitable because of the lack of specific symptoms early in the illness, with a global survival of less than 20% (Lopes and Fagundes, 2012, Zhang *et al.*, 2015).

According to the Brazilian National Cancer Institute (INCA), the estimate of esophageal cancer in 2016 in Brazil is 2,860 cases in women and 7,950 in men (INCA, 2016). The prevalence of esophageal cancer among Brazilian regions is varied, the South region the being 5th most frequent in men, followed by the Central West (6th) and the Southeast and Northeast in 11th (INCA, 2016). For women, the South is the 11th most common, followed by Southeast and Northeast (13th) and the Central West and North in 14th (INCA, 2016). In addition, the Rio Grande do Sul State represents a higher risk for developing ESCC due to factors such as smoking, alcohol, hot foods and hot drinks consumption (Souto Damin *et al.*, 2006, Antunes *et al.*, 2013).

Esophageal squamous cell carcinoma (ESCC)

ESCC and esophageal adenocarcinoma (EAC) are the major types of esophageal cancer; ESCC is the most predominant histologic type found in African-descendent patients and EAC in Caucasians (Lin *et al.*, 2011, Zhang, 2013). EC patients present an overall survival of five years when exposed to treatment (90%), but this rate decreases dramatically (20%) in patients in the late stage (Dawsey, Lewin, Liu*, et al.*, 1994, Dawsey, Lewin, Wang*, et al.*, 1994, Shimizu *et al.*, 2002, Rice *et al.*, 2009, Siegel *et al.*, 2012, Edgren *et al.*, 2013).

There are many risk factors to the ESCC development, such as food intake, hot beverages, smoking habit (most important), high ingestion of red meat, canned foods, achalasia and virus infections, as human papillomavirus (HPV) (Bosetti *et al.*, 2000, Islami *et al.*, 2009, Liyanage *et al.*, 2014).

Human papillomavirus **(HPV)**

HPV Biology

HPV belongs to the *Papillomaviridae* family, which comprise a group of small viral double-stranded DNA that are sexually transmitted among individuals (Jin and Xu, 2015, Lorenzi *et al.*, 2015).

The genome of HPV is divided into three regions (Open Reading Frames - ORF): early (E), late (L) and control region, and a non-coding region. The early region is composed by the *E1*, *E2*, *E4*, *E5*, *E6* and *E7* genes; the *L1* and *L2* genes are responsible for viral reorganization, forming the viral capsid and allowing a new infection to complete their life cycle (Zheng and Baker, 2006). The *L1* gene is responsible for remaking the capsid and the *L2* gene function is to reorganize and rebuild the viral body (Doorbar, 2005). The *E1* and *E2* genes encode important proteins for viral DNA replication and gene transcription. The E4 protein is expressed in the later stages and is important in altering the intracellular matrix, maturation and release of new virus particles. The E6 and E7 proteins are involved in virus amplification. The late regions L1 and L2 encode viral proteins in the later stages of viral replication (Scheurer *et al.*, 2005, Munoz *et al.*, 2006).

The infection cycle occurs in five steps: infection, maintenance of the genome, proliferative phase, genomic amplification and synthesis and release of new viral particles (Doorbar, 2005). There are more than 200 HPV types; based on their capacity to induce cell immortalization these are divided in two groups: low-risk and high risk. (de Villiers, Fauquet*, et al.*, 2004, Zheng and Baker, 2006, Van Doorslaer *et al.*, 2013). HPV as a cause of cervical cancer was first suggested in the 70s by Harald zur Hausen. In addition, HPV infection may contribute to approximately 5% of all human cancers (de Villiers, Fauquet*, et al.*, 2004, Zheng and Baker, 2006, Van Doorslaer *et al.*, 2013).

HPV Oncogenesis

Currently, over 200 HPV (http://pave.niaid.nih.gov/) types are described, are classified in genera β, γ, μ and ν that are involved in the appearance of papillomas and

verrucas (Nguyen *et al.*, 2014). The other genus α-HPV are classified as low (6 and 11, among others) and high-risk (16, 18, 51, 56, 31, 33, 45, etc.) according to the capacity to induce malignant lesions (Li *et al.*, 2014, Jin and Xu, 2015, Lorenzi *et al.*, 2015). The role of high-risk HPV in cervical cancer development is well-defined (Castillo *et al.*, 2011). Among the HPV types, HPV16 and HPV18 are the most frequent, accounting for around 70% of cases (Castillo *et al.*, 2011). The integration of viral DNA in the host cells is one of the factors associated to carcinogenesis, because most cervical cancers contain integrated viral genome fragments (Durst *et al.*, 1987).

HPV-induced cancer is a result of a complex cascade of events that integrate different molecules that affect cell cycle regulation, among other biological phenomena. In brief, the HPV genome integration in the host cells leads to abnormal expression of E6 and E7 oncoproteins (Doorbar, 2005). The E7 oncoprotein interacts with the pRB, displaces the E2F transcription factor, inducing the cell to continue to proliferate uncontrollably (Doorbar, 2005). However, more recently, it has been shown that E2 methylation also limits E2 expression in HPV-related neoplasms (Chaiwongkot *et al.*, 2013). The oncoprotein E6 targets p53 leading to its degradation by preventing DNA repair and apoptosis and positively regulates the expression of telomerase, causing the cells to replicate perpetually (Figure 3) (Doorbar, 2005). Furthermore, the E5 oncoprotein indirectly contributes to the amplification of the genome by altering the environment of the host cell by regulating vascular endothelial growth factor (VGFR) through the EGFR MEK/ERK 1, 2 and PI3K, thus contributing to tumorigenesis (Doorbar *et al.*, 2012, Liyanage *et al.*, 2014, Al Moustafa, 2015).

However it is worth mentioning that the HPV infection model is well defined for cervical and head and neck cancers, but not for ESCC (Doorbar, 2005). In addition, a previous published review by our group addressed the issues related to the disease burden caused by cervical cancer and precursor lesions in Brazil related to HPV (Lorenzi *et al.*, 2015).

Figure 3. Representation of HPV infection in host cell. Adapted from Westra WH (Westra, 2014).

Esophageal cancer and HPV

The role of infectious agents has been suggested as a risk factor for the development of esophageal cancer (Syrjanen, 2002, Liyanage, Segelov*, et al.*, 2013).

Moreover, recent studies suggest that carcinogenesis caused by HPV in cervical cancer is due to the "tropism" that HPV is by residual embryonic cells in the squamocolumnar junction (SCJ) (epithelial cells that book lie underneath the columnar epithelium of the endocervix).These cells and their importance for cervical HPV-induced squamous cell carcinoma (SCC) were identified further to the discovery of residual embryonic cells in the esophogastric (SCJ) (Nguyen *et al.*, 2014, Herfs and Crum, 2015). So it should be emphasized the importance of investigating the presence of HPV in esophageal tissue, since these cells were also found in the esophagus.

Syrjänen and cols. (Syrjanen, 1982) suggested in the early 80s the association between HPV and esophagus cancer in a histological study that showed the presence of HPV in 40% of Finnish patients with ESCC (Syrjanen, 1982).

Estimates of HPV as a risk factor for esophageal cancer vary greatly among different studies (Syrjanen, 2002). This variation may be explained by different sampling methods, anatomical sites, ethnic and demographic factors and the type of methodology used for HPV detection (Li *et al.*, 2014). Therefore the International Agency for Research on Cancer (IARC) has recognized the involvement of HPV in head and neck tumors, but no conclusion has been announced, however, in relation to HPV and ESCC, being necessary more studies in the area (Liyanage, Segelov*, et al.*, 2013).

Techniques used for HPV detection in ESCC

Various techniques have been used in the research field to find HPV evidence in ESCC. In the 1980s the technique often used was *in situ* hybridization (ISH); however, ISH showed a low sensitivity and specificity (Syrjanen, 2002). So, tests with enhanced sensitivity and specificity began to be used as real-time PCR (qPCR) (Xu *et al.*, 2004, Wang *et al.*, 2010, Liu *et al.*, 2012, Antunes *et al.*, 2013, Liyanage *et al.*, 2014). Another method used in HPV identification is the ELISA test (Xu *et al.*, 2004, He *et al.*, 2014).

Schmitt and cols. developed the multiplex HPV genotyping (MPG), which allows the simultaneous detection and genotyping of up to 100 types of HPV in a sample (Schmitt *et al.*, 2006). Additionally, it is a sensitive technique for detection of HPV in clinical samples and is suitable for epidemiological application and diagnosis (Schmitt *et al.*, 2006).

Positive and negative association between HPV and ESCC

Studies in the years 1992 to 2013 reported the presence of HPV in ESCC in Asia and Europe (26.3%) and American countries (14%). Moreover, high-risk regions in China (Anyang, Xinjiang, Sichuan) showed the same correlation between the HPV and ESCC patients. (Cao *et al.*, 2014, Chen *et al.*, 2014, He *et al.*, 2014).

He and cols. (He *et al.*, 2014) analyzed 1,435 samples of patients with ESCC Anyang in China, and showed the presence of the HPV16 E7 oncoprotein with a higher risk of developing ESCC. Chan and cols. screened the HPV types in ESCC patients from Kazakh and Xinjiang regions in China, and showed that the HPV infection accounted for 66.7% and 97.72% HPV16 and 2.27% HPV18 (Chen *et al.*, 2014). Liyanage and cols. performed a case-control study in 99 Australian ESCC patients and 100 healthy individuals and suggested that HPV may be an additional risk factor for the ESCC development (Liyanage *et al.*, 2014). In addition, a recent study of The Cancer Genome Atlas (TCGA) concluded that HPV cannot be considered as an etiological factor for ESCC because of the paucity of HPV mRNA transcripts detectable among ESCCs (Cancer Genome Atlas Research *et al.*, 2017).

According to the study by Evans and cols (Evans *et al.*, 2011), we can classify HPV in "passengers" and "drivers" Driver HPV infections are meaningful in the lesion, however passenger HPV refers to opportunistic infection that is incidental to tumorigenesis may be present in only a few cells within the tumor; suggesting that some techniques, such as PCR, may be inappropriate to associate the presence of HPV as the cause of the tumor (Evans *et al.*, 2011).

The meta-analyses made by Syrjanen (Syrjanen, 2013) show some studies that associate HPV presence in the esophageal mucosa with ESCC according to region, and thus can be observed the high incidence of HPV-positive in ESCC in the regions of China, Japan and Africa, high-risk areas, corroborating what is described in the literature. Moreover, it can also be seen that the regions considered low risk such as Australia, the USA and Italy show the presence of HPV in patients with ESCC, suggesting the importance of further studies on the role of HPV (especially mRNA expression) in ESCC (Table 1). Besides that the meta-analyses show studies that do not associate HPV presence in esophageal mucosa with and without ESCC, the great majority of regions are considered low risk for the development of ESCC (Table 2) (Syrjanen, 2013).

Table 1 - HPV positive in ESCC patients. Adapted from (Syrjanen, 2013).

Author (year and ref.)	Country	HPV types	HPV positive		Method
			n/total	%	
(Xu *et al.*, 2004)	China	16 (E6, E7)	15/18; 16/18	83/89	IHC
(Yao *et al.*, 2006)	China	16, 18	59/82	72	IHC
(Li *et al.*, 1991)	China	16	12/24	50	SB
(Chang *et al.*, 1992)	China	11, 16, 18, 30	8/20	40	SB
(Chang *et al.*, 1990)	China	6, 11, 16, 18	25/51	49	HB
(He *et al.*, 1996)	China	16, 18	37/103	36	SB, PCR
(Brooks *et al.*, 1987)	China	6, 11, 16, 18	22/51	43	ISH
(Chang *et al.*, 1993)	China	6, 11, 16, 18, 30	85/363	23	ISH
(Zhu *et al.*, 2005)	China	16	86/119	72	ISH
(Chang F *et al.*, 2000)	China	6, 11, 16, 18, 30, 53	117/700	17	ISH
(Qi *et al.*, 2006)	China	16, 18	24/60	40	ISH
(Yao *et al.*, 2006)	China	16, 18	23/82	28	ISH
(Chang *et al.*, 1992)	China	6, 11, 16, 18	25/51	49	PCR
(Chen, 1993)	China	CP	24/40	60	PCR
(Chen *et al.*, 1994)	China	GP	24/40	60	PCR
(He *et al.*, 1997)	China	16, 18	32/152	21	PCR
(Lavergne and de Villiers, 1999)	China, S. Africa	CP	19/63	30	PCR
(de Villiers *et al.*, 1999)	China	CP	20/117	17	PCR
(Chang *et al.*, 2000)	China	CP	17/101	17	PCR
(Shen *et al.*, 2002)	China	CP	115/176	66	PCR
(Liu *et al.*, 2003)	China	CP	28/152	18	PCR
(Xu *et al.*, 2003)	China	CP	28/40	70	PCR
(Zhou *et al.*, 2003)	China	CP	31/48	63	PCR
(Si *et al.*, 2003)	China	CP, 16, 18	43/319	14	PCR
(de Villiers, Gunst, *et al.*, 2004)	China	CP	20/30	67	PCR
(Lu *et al.*, 2004)	China	SP, 16	55/104	53	PCR
(Si *et al.*, 2005)	China	SP, 16	35/35	100	PCR
(Liu *et al.*, 2005)	China	SP, 16	24/40	60	PCR
(Cao *et al.*, 2005)	China	CP, 16, 18	207/265	78	PCR

(Continued).

Table 1 - (Continued).

Author (year and ref.)	Country	HPV types	HPV positive		Method
			n/total	%	
(Zhou *et al.*, 2007)	China	SP, 16	97/161	60	PCR
(Liu *et al.*, 2007)	China	16, 18	61/112	50	PCR
(Lu *et al.*, 2008)	China	Various	20/67	30	INNO-Lipa (PCR)
(Yang *et al.*, 2008)	China	SP 16, 18	308/435	71	PCR
(Zhao *et al.*, 2009)	China	CP, SP 16, 18	37/42	88	PCR
(Zhang *et al.*, 2010)	China	SP 16, 18, 58	35/70	50	PCR
(Wang *et al.*, 2010)	China	SP, genotyping	244/435	56	PCR
(Wang *et al.*, 2010)	China	16	35/69	51	PCR
(Ding *et al.*, 2010)	China	GP	8/17	47	PCR
(Zhang *et al.*, 2011)	China	CP, genotyping	82/106	77	PCR
(Cui *et al.*, 2011)	China	16, 18	18/18	100	PCR
(Furihata *et al.*, 1993)	Japan	6, 11, 16, 18, 31, 33	24/71	34	ISH
(Ono *et al.*, 1994)	Japan	16, 18	13/42	31	ISH
(Takahashi *et al.*, 1998)	Japan	6, 11, 16, 18	37/123	30	ISH
(Shibagaki *et al.*, 1995)	Japan	CP	15/72	21	PCR
(Khurshid *et al.*, 1998)	Japan	CP, 16, 18	17/27	63	PCR
(Kawaguchi *et al.*, 2000)	Japan	CP	12/75	16	PCR
(Hasegawa *et al.*, 2002)	Japan	CP	20/48	42	PCR
(Goto *et al.*, 2011)	Japan, Taiwan, Singapore	PC, HR-HPV	17/181	9	PCR, ISH
(Castillo *et al.*, 2011)	Japan, Pakistan, Colombia	SP 16	24/166	14	PCR
(Sobti *et al.*, 2001)	India	CP	25/40	63	PCR
(Katiyar *et al.*, 2005)	India	SP 16, 18	27/101	27	PCR
(Hussain *et al.*, 2009)	India	SP 16, 18	14/75	19	PCR
(Hussain *et al.*, 2011)	India	GP	14/75	19	PCR
(Gupta *et al.*, 2012)	India	CP	17/49	35	PCR
(Cooper *et al.*, 1995)	S. Africa	6, 11, 18, 31, 33	25/48	52	ISH

(Continued).

Table 1 - (Continued).

Author (year and ref.)	Country	HPV types	HPV positive		Method
			n/total	%	
(Williamson *et al.*, 1991)	S. Africa	Various	6/14	43	PCR
(Matsha *et al.*, 2002)	S. Africa	CP, SEQ, 11, 39, 52	23/50	46	PCR
(Kim WH *et al.*, 1991)	Korea	16, 18	16/24	67	PCR
(Farhadi *et al.*, 2005)	Iran	CP, 16, 18	14/38	37	PCR
(Far *et al.*, 2007)	Iran	CP	33/140	24	PCR
(Suzuk *et al.*, 1996)	USA	6, 16, 18	1/23	4	PCR
(Kamath *et al.*, 2000)	USA	CP	1/22	5	Reverse line
(Doxtader EE and L, 2012)	USA	HR-HPV	1/6	17	ISH
(Hippelainen *et al.*, 1993)	Finland	-	11/61	18	HB, ISH
(Syrjanen, 1982)	Finland	-	24/60	40	HB
(Benamouzig *et al.*, 1992)	France	6/11, 16/18	5/12	12	DB
(Kulski *et al.*, 1986)	Australia	11, 13, 16, 18	5/10	50	FISH
(Kulski *et al.*, 1990)	Australia	6, 11, 16, 18	9/39	23	HISTOFISH
(Antonsson *et al.*, 2010)	Australia	CP, genotyping	8/222	4	PCR
(Lambot *et al.*, 2000)	Belgium	CP	1/21	2	PCR
(Acevedo-Nuno *et al.*, 2004)	Mexico	CP	15/17	88	PCR
(Herrera-Goepfert *et al.*, 2009)	Mexico	CP	15/60	25	PCR
(Astori *et al.*, 2001)	Italy	CP, RFLP	8/17	47	PCR
(Tornesello *et al.*, 2009)	Italy	SP	10/36	28	PCR
(Gabor *et al.*, 2006)	Hungary	SP 16, 18, SB	6/26	23	PCR
(Bognar *et al.*, 2008)	Hungary	SP 16, 18	6/26	23	PCR

CP, consensus primers; **DB**, dot blot hybridization; **FISH**, filter in situ hybridization; **GP**, general primers; **HB**, histological biopsy; **HISTOFISH**, histology-filter in situ; **HR**, high-risk types; **HRA**, high-risk area; **IHC**, immunohistochemistry; **ISH**, in situ hybridization; **IS-PCR**, in situ-polymerase chain reaction; **LR**, low-risk types; **PCR**, polymerase chain reaction; **RFLP**, restriction fragment length polymorphism; **SB**, Southern blot hybridization; **SEQ**, sequencing; **SP**, specific primers.

Table 2 - HPV negative in ESCC patients. Adapted from (Syrjanen, 2013).

Author (Year and ref.)	Country	HPV types	HPV negative		Method
			n/total	%	
(Kuwano *et al.*, 2001)	Japan	Ag	0/4	0	IHC
(Akutsu N *et al.*, 1995)	Japan	CP	0/31	0	PCR
(Saegusa *et al.*, 1997)	Japan	CP, 16, 18	0/103	0	PCR
(Loke SL *et al.*, 1990)	Hong Kong	6, 11, 16, 18	0/37	0	DB
(Lu *et al.*, 1995)	China	16, 18	0/35	0	SB, PCR
(Gao *et al.*, 2006)	China	HR	0/4	0	HCII
(Ashworth *et al.*, 1993)	UK	6, 11, 16, 18, 31, 33	0/4	0	ISH
(Morgan *et al.*, 1997)	UK	-	0/22	0	PCR
(De Petris *et al.*, 2005)	USA	Wide spectrum	0/2	0	ISH
(Kiyabu MT *et al.*, 1989)	USA	16/18	0/13	0	PCR
(Paz *et al.*, 1997)	USA	-	0/11	0	PCR
(Baines *et al.*, 2005)	USA	CP	0/22	0	PCR
(Bellizzi *et al.*, 2009)	USA	HR-HPV	0/9	0	ISH
(Malik *et al.*, 2011)	USA	HR-HPV	0/32	0	ISH
(Landau *et al.*, 2012)	USA	HR-HPV	0/9	0	ISH
(Benamouzig *et al.*, 1995)	France	6, 11, 16, 18, 31, 33	0/75	0	PCR
(Benamouzig R *et al.*, 1996)	France	-	0/75	0	PCR
(Regragui *et al.*, 2004)	France	CP	0/1	0	PCR
(Smits *et al.*, 1995)	Holland	CP	0/61	0	PCR
(Kok TC *et al.*, 1997)	Holland	CP	0/63	0	PCR
(Rugge *et al.*, 1997)	Italy	-	0/18	0	PCR
(Talamini *et al.*, 2000)	Italy	CP, 16, 18	0/45	0	PCR
(Poljak M *et al.*, 1998)	Slovenia	CP, 6, 16, 18	0/121	0	PCR
(Lewensohn-Fuchs *et al.*, 1994)	Sweden	GP	0/10	0	PCR
(Awerkiew *et al.*, 2003)	Germany	CP	0/23	0	PCR
(White *et al.*, 2005)	Kenya	Various	0/29	0	INNO-Lipa (PCR)
(Koh *et al.*, 2008)	Korea	16, 18, 31, 33, 35, 52, 58	0/129	0	PCR

Ag, HPV antigens; **CP**, consensus primers; **DB**, dot blot hybridization; **GP**, general primers; **HCII**, hybrid capture 2; **HR**, high-risk types; **IHC**, immunohistochemistry; **ISH**, in situ hybridization; **PCR**, polymerase chain reaction; **SB**, Southern blot hybridization.

In Brazil, a region considered at high risk for the development of esophageal cancer (de Barros *et al.*, 1999), few studies have investigated the presence of HPV in patients with and without ESCC, as shown in Table 3. These studies failed to establish an association between HPV and ESCC, being extremely important more studies to prove the presence of HPV in patients with ESCC.

Table 2 - Brazilian studies that analyzed the presence of HPV in patients with ESCC.

Author (Year and ref.)	HPV types	HPV positive Cases		HPV positive Control		Method
		n/total	%	n/total	%	
(Weston and Prolla, 2003)	HR and LR	1/40	2.5	1/10	10	HCII
(Souto Damin *et al.*, 2006)	CP, SEQ, 16, 18	26/165	16	0/26	0	PCR
(Herbster *et al.*, 2012)	16, 18, 66	34/264	13	-	-	PCR, ISH
(Antunes *et al.*, 2013)	HPV L1	0/52	0	0/122	0	PCR
(Pastrez *et al.*, 2017)	Various	12/87	13.8	12/87	13.8	Luminex

CP, consensus primers; **SEQ,** sequencing**; HCII**, hybrid capture 2; **HR**, high-risk types; **ISH**, in situ hybridization; **PCR**, polymerase chain reaction; **LR,** low-risk types.

HPV and chagasic megaesophagus

The presence of HPV in ESCC patients has been associated especially in high risk areas (Liyanage, Rahman*, et al.*, 2013). It is known that individuals with achalasia have a high risk to develop ESCC (Tustumi *et al.*, 2017). However, the prevalence of HPV in patients with megaesophagus has not been explored (Crema *et al.*, 2010). As far as we know, just one Brazilian study addressed the association between megaesophagus and HPV (Crema *et al.*, 2010). According to Crema *et al*. 63.3% (19/30) of patients HPV positive also presented achalasia and 16.7% (3/18) did not present megaesophagus. The predominant HPV type was HPV16 in 15/22 followed by HPV18 in 4/16 positive patients. In addition, HPV was present in most patients with grades III and IV megaesophagus (Crema *et al.*, 2010).

Conclusion

Considering what was discussed in this review, we observed that esophageal cancer is an aggressive tumor with high mortality in the world, being the squamous cell carcinoma subtype the most frequent, being the knowledge of its risk factors fundamental to aid in prevention strategies and even in the early detection of this malignancy. Among the several risk factors presented, we highlight the megaesophagus of Chagas' etiology (mainly degrees III and IV), and HPV as a possible cause, however its incidence varies greatly between studies. Thus, we have shown that more studies are essential to clarify the association of these risk factors and to better understand the development of the ESCC.

Declarations

The authors declare that they have no competing interests for this review.

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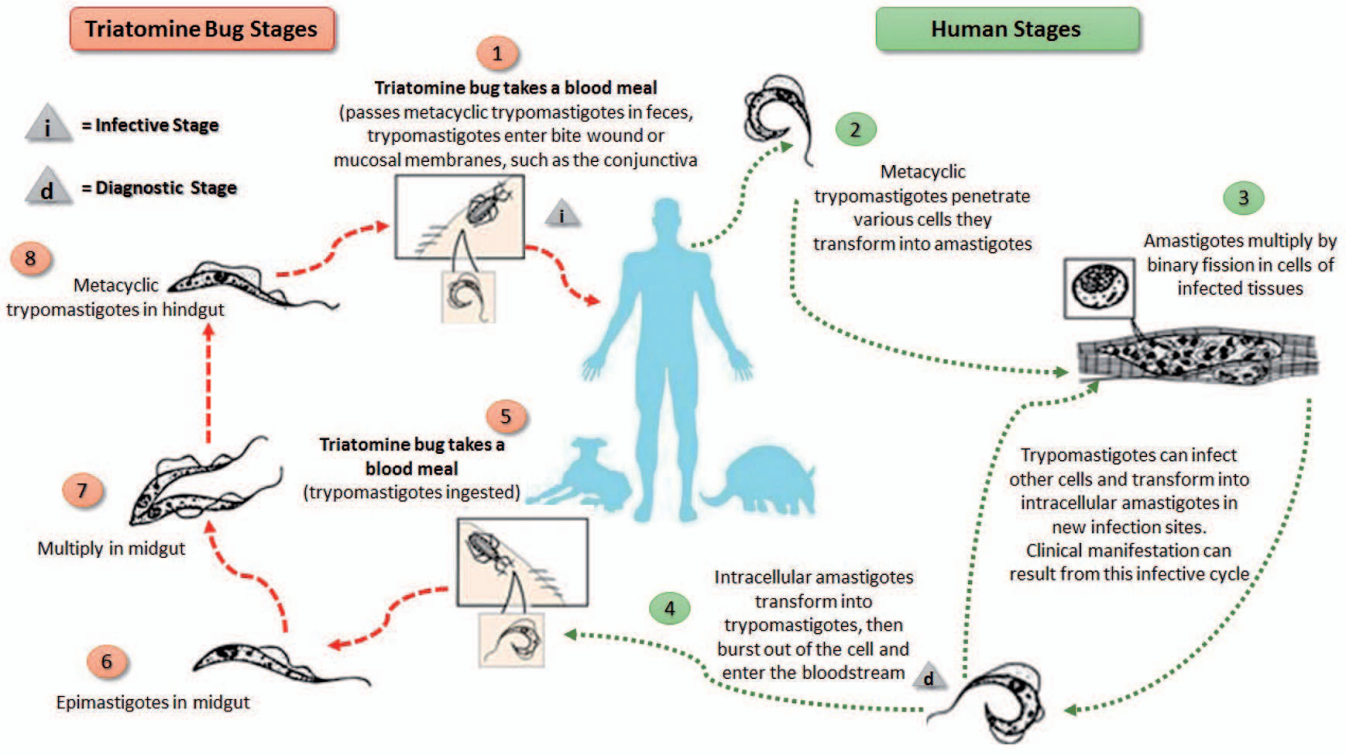
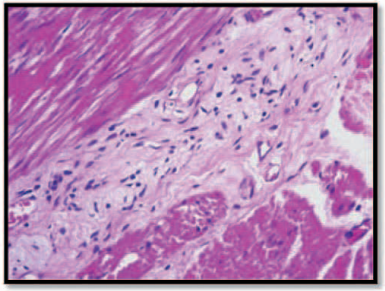
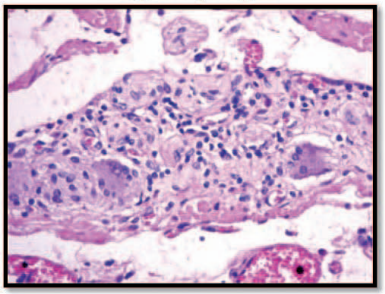

Triatomine Bug Stages
Human Stages
1
Triatomine bug takes a blood meal
(passes metacyclic trypomastigotes in feces, trypomastigotes enter bite wound or mucosal membranes, such as the conjunctiva
i = Infective Stage
d = Diagnostic Stage
i
2
Metacyclic trypomastigotes penetrate various cells they transform into amastigotes
3
Amastigotes multiply by binary fission in cells of infected tissues
Trypomastigotes can infect other cells and transform into intracellular amastigotes in new infection sites.
Clinical manifestation can result from this infective cycle
4
Intracellular amastigotes transform into trypomastigotes, then burst out of the cell and enter the bloodstream
d
5
Triatomine bug takes a blood meal
(trypomastigotes ingested)
6
Epimastigotes in midgut
7
Multiply in midgut
8
Metacyclic trypomastigotes in hindgut

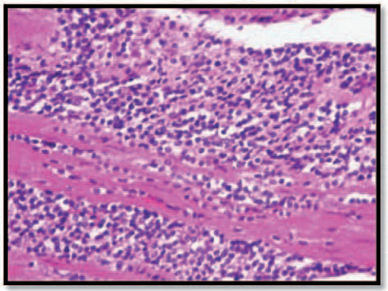
Aganglionosis and fibrosis in myenteric plexus in case of megaesophagus



Mild chronic ganglionitis in esophagus without megaesophagus



Severe chronic myositis in a case of megaesophagus



Severe chronic ganglionitis surrounded by eosinophils in a case of megaesophagus