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Etiological Factors of Esophageal Cancer

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Abstract: Worldwide esophageal cancer is the least studied but one of the deadliest cancer. The exact etiological factors for this increasing incidence of esophageal cancer are enigmatic. Although, some environmental factors such as, smoking, alcohol, obesity, nutritional deficiency etc. have been linked with esophageal cancer. Further research on the causes of esophageal cancer is intensely warranted, which may provide crucial information for preventive strategies. This review article briefly discussed about the incidence, pathogenesis and all possible environmental factors associated with esophageal cancer.

Key words: Adenocarcinoma · Cancer · Esophagus · Etiology

INTRODUCTION

In the World, esophageal cancers ranks amongst the ten most common cancers in the world (over three lakh new cases/year), while new studies showed an increasing incidence. Prognosis of this cancer is very poor with an overall five year survival rate of less than 10% [1]. As esophageal carcinoma is a multifactorial disease; no single factor has been investigated so far as the etiological factors for esophageal cancer. This review article focuses on the incidence, pathogenesis and various risk factors associated with esophageal cancer.

Incidence: In American men, particularly black men, esophageal carcinoma is the 7th foremost cause of death from cancer. Black men have greater incidence of esophageal cancer (thirteen cases per one lakh) as compared to men of other ethnic or racial groups [2]. Esophageal carcinoma worldwide is the 6th foremost cause of death from cancer [3]. In the United States during 2003, 13, 000 deaths and 13, 900 new cases of esophageal cancer including gastro esophageal junction were anticipated [4]. For men and women, the lifetime risk of this cancer is 0.8% and 0.3% [2]. With age the risk increases, with a mean age at diagnosis of 67 years [2, 5].

Pathogenesis of Esophageal Cancer: The exact pathogenesis of esophageal cancer remains unclear. Animal's data suggest that carcinogenic process may be initiated by the oxidative injury from different factors such as, gastro esophageal reflux or smoking, which leads to esophagitis and augmented cell turnover [6]. Once cancer established, it may rapidly spread [7, 8]. More than 50 % of esophageal cancer patients at the time of diagnosis have either radiographically visible metastases or unresectable tumors [9]. In experimental animals, the only esophageal tumor inducing carcinogen reported is nitrosamines. In rodent's esophagus, CYP2A expression studies suggest a link between esophageal susceptibility to tumorigenesis and CYP2A expression. In human, CYP2E1and CYP2A6 are the main enzymes which activate nitrosamines, which in Brazil is the only carcinogen activating CYP enzymes to be expressed in the esophagus. Nitrosamine were activated in patients, who presented high levels of CYP2A6 expression at rates comparable to the rat [10]. In the esophageal cancer, the most frequently oncogenes activated EGFR, Int-2/hst-1, c-myc, 2, FRAT1, c-erbB1 and cyclin D1. These oncogenes are frequently activated by common mechanism such as, over-expression, rearrangement, amplification and point mutations with overexpression

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and amplification the most common [11, 12]. High expression of vascular endothelial growth factors (VEGFs) in esophageal cancer cells leads to stimulation of endothelial migration and proliferation. In contrast to the normal esophageal epithelium, high expression of VEGFs and VEGFRs (receptors) were identified in metaplastic tissues of esophagus in the lower [13].

More than ninety percent of esophageal carcinomas are either adenocarcinomas or squamous-cell carcinomas [5]. On rare occasions, lymphomas, carcinoids, leiomyosarcomas, melanomas and other carcinomas may also develop in the esophagus as well. In the distal region of esophagus, approximately three quarters of all adenocarcinomas are found whereas, squamous-cell carcinomas are more evenly distributed between the lower third and middle part of esophagous [5, 7].

Risk Factors

Smoking: From all over the world, consistent positive associations between cigarette smoking and the development of esophageal cancer were reported [14]. According to the recent evaluation of International Agency for Research on Cancer (IARC), cigarette smoking was evaluated as group 1: carcinogenic to humans [15, 16] thus, confirming that smoking is a potent etiological factor for esophageal cancer. Even sheesha smoking can cause various cancers (including esophagus) [17] and infertility [18]. In tobacco smoke, there are about 7000 chemicals [19] out of which more than 60 are carcinogens [20] derived from various chemical classes such as inorganic compounds, nitro compounds, volatile hydrocarbons, phenols, aldehydes, aromatic amines, nitrosamines (i.e., NNN, NNK,) polycyclic aromatic hydrocarbons (PAHs) and other organic compounds [21]. Nicotine present in cigarette smoke stimulates cancer by activating signaling pathways facilitating invasion, migration, angiogenesis and cellular growth [22]. During the process of smoking or curing, nicotine can be chemically transformed into carcinogens NNN and NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) [23, 24]. Nitrosamines and nicotine activate β-adrenergic receptors (β-AdrRs) and nicotinic acetylcholine receptors (nAChRs) leading to tumor promotion [22].

Alcohol Consumption: The IARC [25] and many other studies [26-29] have concluded that drinking alcohol is a well-known etiological factor of esophageal cancer. A very strong link exists between alcohol addiction and cancers of the mouth, pharynx and esophagus. Similarly, a controversial association links alcohol with breast, liver and colorectal cancers. In the USA, annually more than 125, 000 people are killed by these various form of cancers [30]. The exact mechanism of how alcohol induces carcinogenicity is not known, this is because alcohol itself is unable to bind DNA. Further, it is not mutagenic and is unable to cause cancer in animals [31]. However, some scientists have suggested several mechanisms for its carcinogenicity for example, alcohol may affect oncogenes at the promotion and initiation stages of cancer. Similarly, acetaldehyde, a product of alcohol metabolism, ruins a cell's natural ability to repair its DNA, resulting in a greater likelihood that mutations causing cancer initiation will occur [32]. Very recently it has been suggested that in human cells, alcohol exposure may result in overexpression of certain oncogenes, triggering cancer promotion [33]. Although there is no evidence that alcohol itself is a carcinogen, alcohol may act as a cocarcinogen by enhancing the carcinogenic effects of other chemicals. For example, studies indicate that alcohol enhances tobacco's ability to stimulate tumor formation in rats [34]. In humans, the risk for mouth, tracheal and esophageal cancer is 35 times greater for people who both smoke and drink than for people who neither smoke nor drink [35], implying a cocarcinogenic interaction between alcohol and tobacco-related carcinogens [33].

Yerba Mate Addiction: In southern America, Paraguay, Uruguay, Argentina and Brazil, large volume of maté, which is an infusion of the herb Ilex paraguayensis (yerba mate) is consumed [36]. In 1991, IARC classified hot maté as a probable (Group 2A) carcinogen to humans [37]. Maté is often consumed hot or very hot, causing repeated thermal injury leading to cancer [38]. Further, large amount of PAHs are also found in Ilex paraguayensis leaves [38] and high concentrations of urinary markers of PAHs in maté drinkers [39] confirm the association between mate drinking and esophageal cancer. Maté has also been shown to have mutagenic effects in bacterial assays and to cause chromosomal aberrations in human peripheral lymphocytes treated ex vivo [40].

Hot Drinks and Foods: Recurrent thermal injury to the esophageal mucosa due to consumption of large amounts of hot drinks causing thermal irritation is probably the most constant factor predisposing to the cancer of the esophagus [41]. If hot drinks indeed cause esophageal cancer, they can explain a large proportion of all cases in populations in which drinking tea, coffee, mate or eating hot foods are common [42]. Drinking hot beverages

(and probably food) could substantially increase the intraesophageal temperature and this increase was a function of the initial drinking temperature and, more importantly, the size of the sip [43]. For example, drinking 65°C coffee increased the intraesophageal temperature by 6-12°C, depending on the sip size. These drinks also exert their carcinogenic effects through their chemicals such as, some studies have shown mutagenic effects for tea, coffee and unprocessed mate herb extracts [43].

Carbonated Soft Drinks (CSD): Since in the mid-1970s, the incidence rates for esophageal adenocarcinoma have increased >350% [44]. This might de due CSD use as, both there is a parallel increase in the consumption of CSD and incidence of esophageal adenocarcinoma due to the acidic nature of these drinks (pH<4.0) and their capacity to increase gastric distension [45]. In contrast, some case-control studies have found no [46] or inverse [47] association between CSD and esophagus cancer. Thus the exact role of CSD in esophageal cancer pathogenesis is ambiguous.

Opium Addiction: The study [48] showed that opium use was associated with a 2 fold increased risk of esophageal cancer. Ames test showed that crude opium is not mutagenic [49, 50] however, smoking opium may produce polycyclic aromatic hydrocarbons or other carcinogenic compounds. Opium smoke condensates from opium and morphine cause mutations in S. typhimorium [49, 50] sister chromatid exchanges in human lymphocytes [50] and morphological transformations in cultured Syrian hamster embryo cells [51].

Pickle Vegetables: It has been reviewed by CS Yang that, those areas are at higher risk of getting esophageal cancer that used higher amounts of pickled vegetables [52]. This carcinogenic effect of pickled vegetables might be due to fungi and yeasts that grow in pickled vegetables and release potentially carcinogenic compounds such as N-nitrosamines, Roussin red methyl ester and mycotoxins [52, 53]. Further Ames test showed that sample of pickled vegetables are mutagenic and can cause sister chromatid exchanges in Syrian hamster and can also cause cancer when fed to rats [52, 54-55]. Even IARC evaluation in 1993 concluded that traditional Asian pickled vegetables *are* possibly carcinogenic (Group 2B) to humans [56].

Fruits and Vegetables: Low intake of fresh fruit and vegetables has long been considered as a possible risk factor for esophageal cancer [57]. The large majority of studies found inverse associations between intakes of fruits, especially citrus fruits [57]. Similarly, non-starchy vegetables probably protect against esophageal cancer [57]. Putting all evidence together, high intake of fruit and vegetables probably decreases esophageal cancer risk by approximately 20% per 50 g of fruit or vegetable intake per day [57].

Vitamin and Mineral: For cancers such as upper gastrointestinal tract, selenium deficiency has been reported as a risk factor. Both experimental and observational studies investigated that in selenium deficient populations, higher selenium status reduces the risk of gastric and esophageal cancers [58]. In rodent's esophageal carcinogenesis, zinc deficiency also enhances the effects of N-nitrosomethylbenzylamine and certain other nitrosamines [59, 60]. Human study also reported significant dose-response relationship between lower levels of zinc and increased risk of esophageal cancer [61].

Occupational Exposure: Occupational exposure to asbestos could increase esophageal cancer risk between 2-fold and 16-fold [62]. Similarly, occupational exposure to Silica also increases esophageal cancer risk [63]. Because of their effect in causing lung cancer and mesothelioma, IARC has classified crystalline silica and asbestos as a carcinogenic to humans (Group 1 carcinogen) [64, 65].

Fumonisins: Fumonisins are toxins secreted from Fusarium verticillioides, a fungus that grows mostly on maize. Fumonisin B_1 is a known animal carcinogen and has been shown to cause tumors of the liver and kidney in mice and rats [66]. In South Africa, Iran and China, ecological studies have shown higher exposure to fumonisins in areas with higher risk of esophageal cancer [67-69].

Helicobacter Pylori: The large majority of studies have found a protective role of *H. Pylori* in association with esophageal cancer and the results of three recently published meta-analyses showed that H. pylori colonization of the stomach is associated with a nearly 50% reduction in risk [70-72]. H. pylori colonization might reduce esophageal cancer risk by reducing gastric acid production and hence reducing acid reflux from the stomach to the esophagus [73]. It might also reduce the risk by decreasing ghrelin [74] which leads to lower rates of obesity, an important risk factor for esophageal cancer [75]. H. pylori colonization in the past few decades has been reduced due to widespread use of antibiotics and

advances in sanitation [76]. For example, in United State data from the National Health and Nutritional Examination Survey 1999–2000 indicated the presence of H. pylori in only 5% of children who were born in the 1990's [77], which was far lower than that seen in older people of the United States [77] or than children of other countries with lower socioeconomic status [78]. Therefore it can be concluded that recent increase in esophageal cancer incidence in Western countries might be due to decline in H. pylori colonization.

Human Papillomavirus (HPV): In 1982, HPV was first suspected to have a role in the etiology of esophageal cancer when histological findings suggesting the presence of HPV were observed in benign esophageal epithelia and malignant esophageal tumors [79]. But due to differences in study design, geographic variation, lack of appropriate adjustment for tobacco use or alcohol consumption results are inconsistent [80]. Because of these conflicting results, a recent report by IARC concluded that "there is inadequate evidence in humans for carcinogenicity of HPV in the esophagus" [81].

Medications: A meta-analysis of nine studies concluded that, Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) reduces the risk of esophageal cancer in a dose-response manner [82]. These drugs might reduce risk by decreasing inflammation and at early stages affecting the inflammation-metaplasia-cancer sequence [83].

Drugs such as, cimetidine and ranitidine may reduce esophageal cancer risk by reducing the acid content of gastroesophageal reflux [84]. Similarly, they also neutralizes gastric pH which enhances gastric bacterial population that ultimately leads to carcinogens production such as acetaldehyde and nitrosamines. Further, in the stomach cimetidine can be nitrosated to form nitrosocimetidine, which has a chemical structure similar to the potent carcinogen N-methyl-N'-nitro-N-nitrosoguanidine [84].

Certain medications such as benzodiazepines, nitroglycerin, calcium channel blockers and asthma drugs (β-adrenergic agonists and drugs containing theophylline) relax the lower esophageal sphincter and hence may promote acid reflux and higher risk of esophageal cancer [85].

Tooth Loss and poor Oral Hygiene: A lot of studies have reported that the incidence of esophageal cancer were statistically significant in a population suffering from either tooth loss or poor oral hygiene as compared to control population [86-89]. Poor oral hygiene might alter microbial flora that may leads to higher carcinogens production such as acetaldehyde and nitrosamines. Or this might be due to chewed food that damage esophageal epithelium or this might be due alteration in dietary patterns and nutrient intake due to poor dentition.

Aldehyde Dehydrogenase 2 (ALDH2) Deficiency: Deficiency in the enzyme ALDH2, which causes so-called alcohol flushing response, has been revealed to increase the risk of alcohol-related ESCC [90]. In East Asian populations, there is a variant of ALDH2, resulting from the replacement of glutamate at position 487 with lysine, with the lysine allele encoding an inactive protein [91].

Gastroesophageal Reflux Disease (GERD): The strongest known risk factor for esophageal cancer is gastroesophageal acid reflux. At least weekly symptoms of GERD increases the odds of esophageal adenocarcinoma five-fold, while daily symptoms increased the odds seven-fold, when compared with those with less frequent episodes [92]. In Sweden, Lagergren and colleagues [93] in a population-based case-control study, reported a strong dose-response association of both duration and frequency of reflux with esophageal cancer.

Gastric Atrophy: The major feature of pernicious anemia (PA) is gastric atrophy and patient with PA had a 3-fold higher risk of ESCC than the general population [94]. In gastric atrophy, gastric glands disappear causing decreased acid secretion and ultimately leads to bacterial proliferation in stomach [95]. Further, these bacteria might increases carcinogens productions such as nitrosamines and acetaldehyde.

Hiatus Hernia: A lot of studies have concluded the association between hiatus hernia and esophageal cancer and all have reported high risks, with relative risks ranging 2–6-fold [96, 97].

Achalasia: Due to achalasia, in esophagus there is stasis and fermentation of boluses, which increases esophageal inflammation and higher cancer risk [98]. The largest cohort study in Sweden reported a 10-fold increased risk of both esophageal adenocarcinoma (EA) and ESCC in achalasia patients as compared to the rest of the population [99].

Obesity: In obese and overweight individuals, esophageal adenocarcinoma risk increases approximately 2–3-fold. Further it was also found that, risk in obese was slightly higher as compared to overweight individuals [100]. In Western countries, increase in the incidence rate of esophageal cancer may be due to increasing weight trends in these countries [101]. Obesity might increases the risk by increasing the risk of gastroesophageal reflux through increasing intra-abdominal pressure [102] or it may modulate the levels of polypeptides such as insulin-like growth factors, adiponectin, leptin and ghrelin, leptin [101].

Socioeconomic Status: According to Watson, esophageal cancer is the disease of poor as nine out of ten patients with esophageal cancer belong to lower middle class and also on the whole are financially insecure [41]. Similarly, a lot of studies reported a strong link between low socioeconomic status and establishment of esophageal cancer [103-105].

History of Thoracic Radiation: Radiotherapy for thoracic diseases, such as breast cancer and Hodgkin's lymphoma, increases the risk of both ESCC and EA [106].

Estrogen Hormone: Although an inhibitory effect of estrogen in the growth of esophageal cancer cells has been reported, there is no firm conclusion on the role of estrogen in human esophageal cancer etiology [107].

Family History: The familial form of ESCC is rare, although familial aggregation has been reported in a high incidence area in China [108]. In contrast, familial clustering of Barrett's esophagus and EA has been observed. In a European cohort study, 7% of cases of Barrett's esophagus and AC were familial [109].

CONCLUSIONS

In this review, different possible risk factors associated with esophageal cancer progression were discussed in details. Different studies suggested that smoking, alcohol, mate drinking, carbonated drinks, hot drinks and foods, opium, pickle vegetables, low intake of fruits and vegetables, mineral deficiency, occupational exposure to asbestos and silica and fumonisins can cause esophageal cancer. Similarly certain other factors such as, H. Pylori, HPV, certain medications, poor oral health and tooth loss, ALDH2 deficiency, GERD, gastric atrophy, hiatus hernia, achalasia, obesity, radiation exposure, socioeconomic status and family history are also positively link with esophageal cancer. In spite of advances in the diagnostic tools and therapeutic strategies, esophageal cancer still remains one of the most lethal malignancies. In order to improve outcomes, identifying all possible etiological factors, early detection of cancers and identifying novel therapeutic targets through molecular biological techniques are crucial.

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