[Frontiers in Bioscience E4, 351-357, January 1, 2012]

The role of nutrition in the development of esophageal cancer: what do we know?

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1. ABSTRACT

Cancer of the esophagus is the eighth most common cancer by incidence worldwide and ranks sixth as the most common cause of cancer death. It is unique among the gastrointestinal tract malignancies because it embodies two distinct histopatologic types, squamous cell carcinoma and adenocarcinoma. Which type of cancer occurs in a given patient or predominates in a given geographic area depends on many variables, including individual lifestyle, socioeconomic pressures, environmental factors and diet and nutrition. Generally for both squamous cell carcinoma and adenocarcinoma of the esophagus case-control studies provide evidence of a protective effect of fruits and vegetables. Here we review the role of nutrition in the etiology of esophageal cancer.

2. INTRODUCTION

Cancer of the esophagus (EC) is the eighth most common cancer by incidence worldwide and ranks sixth as the most common cause of cancer death (1). More than 90% of ECs are either squamous-cell carcinomas (ESCC) or adenocarcinomas (EAC) (2). On rare occasions, other carcinomas, melanomas, leiomyosarcomas, carcinoids, and lymphomas may develop in the esophagus as well. Approximately three quarters of all adenocarcinomas are found in the distal esophagus, whereas squamous-cell carcinomas are more evenly distributed between the middle and lower third (2-3). The incidence of EAC has been increasing rapidly in most western countries during the past three decades, particularly among white males, on the contrary ESCC occurs at relatively high frequency in many

Table 1. Risk factors affecting the development of ESCC

Risk Factors	Strong	Moderate	Low
Tobacco smoking	Yes	No	No
Alcohol abuse	Yes	No	No
Barrett's esophagus	No	No	Yes
Symptomatic GERD*	No	No	Yes
Obesity	No	No	Yes
Excess of Fat consumption	No	No	Yes
Low consumption of F&V°	No	No	Yes
HT^ foods & beverages	No	Yes	No

*GERD: gastroesophageal reflux disease; °fruits and vegetables; ^high temperature.

Table 2. Risk factors affecting the development of EAC

Risk Factors	Strong	Moderate	Low
Tobacco smoking	No	Yes	No
Alcohol abuse	No	Yes	No
Barrett's esophagus	Yes	No	No
Symptomatic GERD*	Yes	No	No
Obesity	No	Yes	No
Excess of Fat consumption	No	Yes	No
Excess of Meat consumption	Yes	No	No
Low consumption of F&V°	Yes	No	No
HT^ foods & beverages	No	No	Yes

*GERD: gastroesophageal reflux disease; °fruits and vegetables; ^high temperature

developing countries (4). Risk factors for both histological types differ substantially. Some recent epidemiologic studies distinguish the histological types of EC, but in many earlier studies this was not the case, and presumably these studies included mostly ESCC cases (5). The risk factors for ESCC are shown in Table 1.

The rapid increase of EAC in Western countries is believed to be attributable to the commensurate increased prevalence of gastroesophageal reflux disease (GERD) and its major determinant, obesity. Risk factors for EAC have been reviewed extensively (Table 2).

The pathogenesis of EC remains unclear. Data from studies in animals suggest that oxidative damage from factors such as smoking or gastroesophageal reflux, which cause inflammation, esophagitis, dietary habits and increased cell turnover, may initiate the carcinogenic process (6).

3. ALCOHOL

Besides smoking, alcohol drinking is an important risk factor with a clear dose-response relationship for esophageal cancer, specifically for the squamous cell type (ESCC). In western countries, about 90% of ESCC is caused by a combination of alcohol and tobacco smoking. In a recent meta-analysis for esophageal cancer, including 27 case-control studies and one cohort study, an increased risk of esophageal cancer was found beginning at two alcoholic drinks per day (7). A Japanese cohort study, not included in the meta-analysis, found a relative risk of over two for death due to esophageal cancer for people drinking alcoholic beverages four or more times per week (8). This increased risk is not limited to particular types of alcoholic beverages (e.g. calvados), but occurs with any type of alcoholic beverages, suggesting that this increased risk is attributable to alcohol itself (ethanol). Nevertheless, several studies have observed higher risk among consumers of stronger drinks, and therefore an additional risk increase due to specific contaminants cannot be ruled out. Alcohol drinking and tobacco smoking act synergistically in increasing the risk of ESCC. The risk of EAC is not or only weakly related to alcohol drinking (Table 1) (9-13).

Many studies have demonstrated a clear relationship between the alcohol consumption and the risk of ESCC (14-15).

More recently the EPIC study confirmed a clear correlation between the high consumption of alcohol and the risk of ESCC for both sexes (16). On the basis of baseline alcohol intake the risk increases per 10 g increase were 1.4 (95% CI 1.11 – 1.18) in men, 1.23 (CI 1.11 – 1.36) in women, and 1.15 (CI 1.12 – 1.18) for both sexes confirmed. Lindbland M, *et al* demonstrated that consumers of more than 34 units of alcohol per day were at a more than three-fold increased risk of ESCC (OR 3.39, 95% CI 1.28-8.99) (13).

4. MEAT AND DIETARY FAT INTAKE

Studies on the relationship between meat intake and esophageal cancer risk have shown varied results potentially related to adequacy of overall nutrient intake. One study in Uruguay showed a significantly decreased risk with meat intake, which is consistent with findings in a Chinese cross-sectional survey(17-18). However, a second study in Uruguay showed an increased risk of esophageal cancer (19). Studies conducted in the United States and Europe have generally found a significant increase in risk only among subjects consuming the highest level of meat (>75 g/d) (20-22). Moreover an increased risk has also been observed for salted meat intake(19). However the consumption of meat and fat are usually related to the risk of EAC.

Zhang ZF, *et al* demonstrated a clear relationship between the high ingestion of processed meats (bacon or

sausage, lunch meat, hot dogs, and other pork or ham) and fat (especially who had high intakes of saturated fat or oleic acid), and elevated risk of EAC (23). A large cooperative and prospective study showed non-statistically significant positive associations between the risk of esophageal adenocarcinoma and intakes of total meat and processed meat and a potential association with poultry intake. Several plausible mechanisms have been suggested to explain the possible causal relationship between meat intake and cancer risk (24). These mechanisms involve potential effects of high levels of heme (a red organic pigment containing ferrous iron) in red meats, of fat and protein, of nitrite and nitrosamines, and of salt, as well as of heterocyclic amines and polycyclic aromatic hydrocarbons. One study (24) showed that red meat intake had a consistent dose response on the endogenous formation of n-nitroso compounds measured in fecal samples, whereas white meat intake had no effect. This effect seems to be associated with the content of heme, rather than with the content of protein or inorganic iron (25). Processed meat is a mixed category that consists mainly of pork and beef product and is an important source of salt, nitrites, and exogenous nitrosamines in the human diet (26).

5. NITROSAMINES

Humans are exposed to a wide range of N-nitroso-compounds (NOCs) from diet, tobacco smoking, work place and drinking water which are the major source of exposure in the general population (26-29). Performed exogenous nitrosamines are found mainly in the cured meat products, smoked preserved foods, foods subjected to drying by additives such as malt in the production of beer and whiskey, pickled and salty preserved foods (27). Available data suggest that nitrosamines are found more frequently and at higher concentration in Asian foods than in Western foods (30). On the other hand, nitrosamines are formed endogenously from nitrate and nitrite. Nitrite is also formed in the human body from oral reduction of salivary nitrate. Vegetables and water are the main sources of nitrate intake. Nitrites are transformed into nitric oxide by gastric acid-catalysed formation, which acts as an nitrosating agent of amines and amides, as consequence of NOC (27). Under chronic inflammatory conditions, such as precancerous conditions of gastric cancer (GC) and EC, nitrosating agents are overproduced (28). Studies in volunteers have shown that red meat intake has a consistent dose response in the endogenous formation of NOC measured in faecal samples, while white meat intake has no effects (31-32).

So far, there is no conclusive epidemiological evidence that nitrosamines are carcinogenic to humans, although they produce a wide range of tumours in more than 40 animal species tested (33). Two important nitrosamines, namely N-nitrosodiethylamine (NDEA) and N-nitrosodimethylamine (NDMA), classified as probably carcinogenic to humans (group 2A) by Internetional Agency for Research of Cancer (IARC) (34).

Ward MH, *et al* demonstrated a significant positive trend in risk of EAC with increasing intake of nitrite plus nitrate from animal sources but not in their cohorts, although based an small numbers of exposed cases (35).

Nitrosamines have been shown to cause a wide range of tumors in more than 40 animals species and many be specifically involved in the etiology of GC and EC, although so far, there is no conclusive epidemiologic evidence that these compounds are related to cancer risk in humans (36). Although the levels of sodium nitrite in foods have decreased during the last 20 years, it is still widely used as a food preservative in cured meat (29). Nitrites and nitrates can nitrosate amines and amides, thus forming potentially carcinogenic N-nitroso compounds (27). Nitrosating agents are overproduced under chronic inflammatory conditions, a common step in the gastric precancerous process (28). In summary, prospective studies with long follow-up periods and validated methodologies quantifying all sources are needed to confirm the role of NOC in esophageal carcinogenesis and to date the evidence in relation with EC is insufficient (30-31).

6. FRUITS AND VEGETABLES

Data on the risk of EC and intake of Fruits and Vegetables are controversial, however their consumption should have a protective effect (relative risk [RR] = 0.3 – 0.8) (15,18-21,36-38).

However more than 30 case-control studies, often hospital-based, have been published on fruit intake and esophageal cancer. A recent IARC report concluded from the case-control studies that the mean OR was 0.54 (95% CI 0.48-0.61), range 0.14-1.50, comparing subjects in high intake categories with subjects in low intake categories (39). Only three cohort studies have been reported, two from China and one from Japan. A borderline significant inverse association was found with total fruit intake in Japan (40). No associations were found in the Chinese studies, however (41-42). Regarding vegetables, IARC arrived for the case-control studies at a mean OR=0.64 (95% CI 0.57-0.72), range 0.10-0.97 (39). Four cohort studies were conducted in China or Japan. The Japanese studies found no association, whereas the Chinese studies reported (borderline) significant inverse association with vegetables (40-41,43). Few case-control and no cohort studies have been reported on EAC specifically; the IARC report did not indicate clear differences in associations between EAC and ESCC, however.

To note pickled vegetables that have been studied for their association with cancer mainly in Asia and especially in the People's Republic of China. The pickling process is different from that used in many parts of the world and uses no salt or vinegar. Instead it relies on natural fermentation and can lead to contamination with mold (44).

A small amount of laboratory evidence suggests that these vegetables may contain mutagens (45-46). Epidemiologic studies have suggested an increased risk of esophageal cancer in pickled vegetable consumers (47-48). In the highest esophageal cancer risk area of north central China no association between pickled consumption and

cancer has been noted in multiple studies (43,49-50). This population was subject to a public health campaign against the consumption of these vegetables prior to the baseline interview. This may have led to exposure misclassification if subject recently discontinued consumption or prevarication due to the repeated warnings to stop the consume of pickles.

7. MICRONUTRIENTS

High intake of antioxidants, such as vitamins C and E, selenium and beta-carotene, may have a protective effect on the risk of upper gastrointestinal cancer. Antioxidants have the potential to neutralize the harmful effects of DNA-damaging free radicals, such as those produced by smoking, and these nutrients have generally emerged as protective factors in previous studies of ESCC and unspecified EC (50-51).

Laboratory studies have suggested many mechanisms whereby micronutrients commonly found in vitamin and mineral supplements could prevent, or promote, cancer. What follows is a very brief overview of some of the plausible mechanisms. Most attention has focused on the antioxidant micronutrients: carotenoids, vitamins C,E, selenium, and zink (52-56).

Many functions have been proposed for antioxidants, including protection of cell membranes and DNA from oxidative damage, scavenging and reduction of nitrites, and serving as cofactors for enzymes that protect against oxidative damage (57). However, pro-oxidant effects for several of these vitamins and minerals have been also suggested (58). Vitamin A (i.e., retinol) plays a role in the differentiation of normal epithelial cells and the maintenance of intercellular communication through gap junctions, thus repressing the processes leading to abnormal cell replication (59). Vitamin C enhances immune response and connective tissue integrity (57).

Terry P, *et al* demonstrated that higher intakes of antioxidants were associated with decreased risk of EC (6). In fact the subjects that had the highest parallel intake of vitamin C, alpha-tocopherol, and beta-carotene, showed 40-50% decreased risk of EC compared with subjects with the lowest parallel intake.

8. TEA INTAKE

Results from animal studies suggest that intake of the polyphenolic compounds found in the tea reduces tumor growth (60). Data on the risk of EC related to the consumption of tea are limited and controversial. In fact Ishikawa A, *et al* demonstrated in a nested case-control study (about 19,000 subjects analyzed) an increased risk of EC in subjects consuming higher amounts of green tea (61). Three out of five retrospective studies found a positive association between the consumption of green tea and the risk of EC (62-64). In two of these studies this association was restricted to female subjects. In the remaining two case-control studies there was no association between drinking green tea and the risk of EC (65-66).

In summary evidence is insufficient to support any conclusions on the relationship between tea intake and EC risk, and further researches are necessary.

9. OTHER RISKS

The research focusing on the role of carbohydrates in EC is limited. Several case-control studies have reported an increased risk of EC with carbohydrate intake in the form of maize, cereals and refined grains, and tubers (18,21). Total percentage of energy intake from carbohydrate has also been associated with increased risk in EC (21,67). Higher carbohydrate diets and excessive energy consumption are commonly associated with lower intake of fruits and vegetables, which may increase EC risk.

Also the consumption of hot beverages has been suggested as a risk factor for EC. Thermal injury may cause EC via both direct and indirect pathways. Inflammatory processes associated with chronic irritation of the esophageal mucosa by local hyperthermia might stimulate the endogenous formation of reactive nitrogen species, and subsequently, nitrosamines. Thermal injury can also impair the barrier function of the esophageal epithelium, which may increase the risk of damage from exposure to intraluminal carcinogens (68). In any case, already in the late 1939, Watson WL, demonstrated a correlation with thermal irritation of esophageal mucosa as risk factor in EC in a 771 cases of EC described (69).

Successively Castellsague X, et al demonstrated a higher risk of EC, in a South America cohort, correlated to consumption of high temperature foods (70).

More recently a review by Islami F, et al, analyzing 77 relevant articles concluded that there was a strongly association between the consumption of high temperature beverage drinking and risk of EC and for other hot foods there was some evidence showing increased risk of EC (71).

10. CONCLUSIONS

The evidence for a link between diet and EC is controversial. Patterns of evidence suggest that diets rich in vegetables and fruit and poor in fat may afford some level of protection. Such micronutrients such as folate, calcium, and vitamin C, D may also be protective. An 86% reduction risk of aerodigestive tract cancers has been estimated to be achievable with avoidance of tobacco and alcohol and increased fruit and vegetable consumption a 20% reduction can be attributed to dietary change alone (72-74). Phase III diet interval trials are necessary before any definitive conclusions can be drawn.

11. ACKNOWLEDGMENTS

The authors would like to thank Daniela Furlan for her expert assistance in the revision and preparation of the manuscript.

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Key Words: Nutrition, Cancer, Esophageal, Risk, Review

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