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The Association of Consumption of Animal Proteins and the Risk of Esophageal Cancer

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ABSTRACT

Aim: Esophageal cancer (EC) is considered one of the most common types of cancer in the world. High intake of dietary proteins is suggested to increase EC. This study examined associations between intake of red meats, processed meat, poultry, and fish and the risk of EC.

Methods: This hospital-based Case–Control study included 96 people with EC and 187 people without EC from Bojnurd, Iran. Socio-demographic data was collected from all participants at enrollment using general information questionnaire. Dietary intake was assessed using a validated 168 item semi-quantitative food frequency questionnaire.

Results: After adjusting for potential confounders, there was a significant association between the consumption of beef ($P = 0.04$), processed meats (sausages) ($P = 0.01$), and chicken with skin ($P = 0.001$) with the risk of EC.

Conclusion: We observed a positive association between red meat, processed meats (sausages), chicken with skin and the risk of EC. The use of lamb meat and fish had no significant association with the risk of EC.

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Introduction

Esophageal cancer (EC) is the eighth most common type of cancer and the sixth leading cause of death from cancer worldwide (1,2). Esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) are two major histologic subtypes of EC. The incidence rates of EAC have risen dramatically in the United States and Western Europe along with a decrease of ESCC in most of these countries (3,4). ESCC was responsible for 90% of all EC particularly in high-risk countries such as China and Iran (5). Large variation in mortality is reported in different geographical areas. Western countries, have reported that mortality rate is less than 5 per 100,000 in men and 1 in 100,000 women, While much higher rates in the north-central China, Africa, Iran, and France (6). Risk factors associated with EC include a family history of cancer, diet quality, and genetic factors (5,7).

Epidemiological studies have explored the association of intake of red and processed meat and risk of EAC and ESCC with mixed results (8–10). Many studies report that there is a significant association between red meat rich diet and EC. Previous analyses estimated that 2.7% of all cancers in 2010 attributed to the consumption of red meat. World Cancer Research Fund recommends limiting consumption of meat <500 g/wk for cancer prevention (11). This association attributed to several dietary factors, including heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAH) produced during high temperature heating processes, and N-Nitrosamines that are found in many processed meat such as sausages (6,12). Also, studies have shown that nitrosamines are

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found more frequently and at higher concentration in Asian food than in the Western food region (13).

Most of the previous studies investigated the association between dietary patterns and EC mortality in Western countries. However, few studies have examined the relationship between dietary patterns and EC in middle-east countries. EC is one of the most common health problems in the North Khorasan region. This study aimed to determine whether red and processed meat associated with the risk of EC mortality among Iranian populations.

Methods and Materials

Study Population

This hospital-based Case–Control study was carried out in North Khorasan Province, Iran. We selected patients with squamous cell carcinoma (SCC) who had been hospitalized in Imam Reza hospital of Bojnurd city. We selected from March 2015 to February 2016. In total, 96 people with EC (as the case group) and 187 people without EC (as the control group) were investigated. Exclusion criteria of both groups were: age $<$ 18 years, and a history of cancer in other organs. The control groups selected from patients who admitted to other wards of the hospitals. They were matching by gender and age with the maximum difference of five years (±5 years) than patients in their age. After explanation of the goals and method of the study, all consent forms were received. The information was collected from the patients through the face to-face interview. The protocol of the study was reviewed and approved by the Ethics Committee of North Khorasan University of Medical Sciences, Bojnurd, Iran

General Information

Information about the province, city or village of residence, age, race, educational level (Academic or non-academic education), family history of cancer and the socio-economic level was collected by completing the general information questionnaire. We used multiple correspondence analyze (MCA) to obtain socioeconomic score. The scores were calculated and categorized to three Quantile (first, second, and Third quantile)

Dietary Assessment

Dietary intake of all participants was assessed using a validated food frequency questionnaire (FFQ) including 168 food items that was previously validated (14). In epidemiologic studies, FFQ is the most appropriate way to evaluate long-term diet plans. It is easy to use and relatively inexpensive. The best possible tool for classifying people based on levels of food intake.

For each food item consumed, participants were asked to indicate the portion size, and the number of servings and the frequency of consumption. Face-to-face interviews were performed by a trained dietitian. In the control group was asked about dietary intake during one year ago before this study. The case group was asked about dietary intake during one year before the onset of symptoms (such as dysphagia).

Statistical Analysis

Data were analysis by PASW18 software. We used chi-square test, ANOVA, and MCA to obtain socioeconomic score. Finally, we analyzed the data using multivariate logistic regression method to identify effect of dietary factors on EC and eliminate the effect of confounding factors. Variables with a significant level below 0.2 were introduced into the multivariate logistic regression model at the same time as other variables.

Results

In this study, 96 people with EC and 187 people without EC were participated. The average age of the case and control groups were 60.7 ± 11.2 and 60.8 ± 11.3 years, respectively which were not statistically significant ($P = 0.9$). Most of the participants in both groups had low literate education, and 46.7% of cases and 15.4% of controls had low socio-economic level. Table 1 shows demographic, behavioral characteristics and socio-economic status of participants.

As shown in Table 1, there was an inverse significant relationship between the socioeconomic level and the risk of esophageal cancer, so that people with a higher socioeconomic level were less likely to had esophageal cancer ($P < 0.05$).

There was also a significant relationship between the risk of esophageal cancer and race (OR = 6.2 CI = 2.9–13.2)

Also in this study it was not found significant relationship between socio-economic status and the average of meat consumption in two study groups ($P = 0.07$). But the average of meat consumption in the Turkmen (1.6 ± 2.5) was significantly higher than non-Turkmen (0.6 ± 1.03) ($P < 0.001$). Table 2 shows the relationship between ECs with consumption of meat in the two study groups.

As shown in Table 2, the consumption of beef and rolled meat had a significant relationship with the risk

Table 1. Socio-economic status and baseline characteristics for control and EC cases.

Variables		Case (*F*%)[a]	Control (*F*%)[a]	Odds ratio (95% CI)	*P*-value
Age	<55	30 (31.3)	59 (31.6)	1	
	55–64	35 (36.5)	64 (34.2)	1.07 (0.5–1.9)	0.8
	65–74	22 (22.8)	37 (19.8)	1.1 (0.5–2.3)	0.6
	≥75	9 (9.4)	27 (14.4)	0.6 (0.2–2.5)	0.3
Sex	Male	42 (43.7)	81 (43.3)	1	
	Female	54 (56.3)	106 (56.7)	0.9 (0.5–1.6)	0.9
Educational level	Under diploma	93 (96.9)	184 (98.3)	1	
	Diploma and higher	3 (3.1)	3 (1.7)	1.9 (0.3–9.6)	0.4
Race	Non Turkoman	68 (71)	175 (93.8)	1	
	Turkoman	28 (29)	12 (6.2)	6.2 (2.9–13.2)	<0.001*
Family history of cancer	No	69 (71.9)	48 (25.7)	1	
	Yes	27 (28.1)	139 (74.3)	1.1 (0.6–1.9)	0.6
Socio-economic status	Low (first quartiles)	45 (46.7)	29 (15.4)	1	
	Middle (Second quartiles)	29 (30)	84 (45)	0.2 (0.1–0.4)	<0.001*
	High (Third quartiles)	22 (23.3)	74 (39.6)	0.1 (0.09–0.3)	<0.001*
Smoking	No	72 (75)	145 (77.5)	1	
	Yes	24 (25)	42 (22.5)	1.1 (0.6–2.04)	0.6
Tobacco consumption	Never	72 (75)	144 (77)	1	
	Current consumption	12 (12.5)	13 (7)	1.8 (0.8–4.2)	0.1
	Previous consumption	12 (12.5)	30 (16)	0.8 (0.3–1.6)	0.5
Alcohol consumption	No	93 (96.9)	182 (97.3)	1	
	Yes	3 (3.1)	5 (2.7)	1.1 (0.2–5.02)	0.8

*Significant at 95% confidence level.
[a]Frequency and percentage.

of esophageal cancer, so that the consumption of more than 4 times in week increased the risk of esophageal cancer respectively 3.5 and 3.8 times.

Also, taking 2–4 times rolled meat per week had a preventable role in the risk of esophageal cancer (OR= 0.2, CI = 0.07–0.9)

Sausage consumption more than twice a week was associated with an increased risk of esophageal cancer and weekly consumption of chicken with skin more than four times increases the risk of esophageal cancer 2.1 times. However, no significant relationship was found between the consumption of lamb meat and skinless chicken with the risk of esophageal cancer ($P > 0.05$)

Discussion

In this study, it was significant association between the consumption of beef, processed meats (sausages), chicken with skin and the risk of EC. So, in which the risk of EC, increased respectively, 3.5, 2.1, and 1.5 times.

The exact mechanism through which beef meat consumption is involved in the development of EC is not well understood yet. Meat is also an important source of fat. Such studies show that fat is associated with an increased risk of EC. The saturated fat and meat with carcinogenic compounds including HCAs and PAHs chemicals cause mutations, which are formed during high temperature cooking process and suggested to play a role in the carcinogenic process (15,16).

Nitrate and nitrite are found in high concentrations in some foods and they are often used as food additives in processed meats. A high Intake of processed meats increased EC risk. Nitrosamines as the main reason for that (17) in this study, processed meats with nitrite and nitrate increases the risk of EC, such studies had reported similar results (17–19). This study show that an increased EC risk in subjects with high processed meat intake, this finding is consistent with a meta-analysis of three cohort and 15 case–control studies finding a 30% increase risk of EC (RR of 1.32, 95% CI 1.08–1.62 (20). Rolon et al. reporting a huge risk of 4.7 for red meat and EC but processed meat intake were not investigated (21).

This study showed that the consumption of chicken with skin, increases risk of EC by 2.1- to two fold. Two cohort studies had shown that the chicken intake increased the risk of cancers (22,23). Those who frequently eat chicken have a lower risk of cancer than those who consume very little chicken (RR= 0.47 and 0.82 in men and women respectively). Similarly, Marchand et al. in one case–control study finding the intake of chicken without skin was negatively associated with risk in both genders (24). In some study observed statistically significant positive associations between chicken consumption with skin and risk cancer progression (25,26).

Richman et al. observed greater consumption of poultry with skin was associated with 2-fold increases in risk cancer in a comparison of extreme quintiles (HR: 2.26; 95% CI: 1.36–3.76) and Consumption of poultry without skin was not associated with risk of cancer progression (26). The poultry with skin is rich in HCA. The poultry with skin may be more broiled and grilled than poultry without skin, which results in

Table 2. Meat intakes in control and EC cases.

Meat group consumption		Case *F* (%)	Control *F* (%)	Odds Ratio (95%CI)	*P*-value[a]	*P*-value[b]
Beef (weekly)	No	27 (28.1)	64 (34.2)	1		
	≤1	42 (43.8)	89 (47.6)	1.1 (0.6–1.9)	0.70	0.23
	2–4	21 (21.9)	30 (16)	1.6 (0.8–3.3)	0.16	0.09
	≥4	6 (6.3)	4 (2.1)	3.5 (0.9–13.6)	0.06	0.04*
lamb meat (weekly)	No	21 (21.9)	29 (15.5)	1		
	≤1	42 (43.8)	98 (52.4)	0.5 (0.3–1.1)	0.12	0.38
	2–4	24 (25)	45 (24.1)	0.7 (0.3–1.5)	0.42	0.87
	≥4	9 (9.4)	15 (8)	0.8 (0.3–1.2)	0.71	0.26
Rolled meat (weekly)	No	54 (56.3)	69 (36.9)	1		
	≤1	36 (37.5)	102 (54.5)	0.4 (0.2–0.7)	0.003*	<0.001*
	2–4	3 (3.1)	15 (8)	0.2 (0.07–0.9)	0.03*	0.002*
	≥4	3 (3.1)	1 (0.5)	3.8 (0.3–37.8)	0.25	0.008*
Weekly consumption of chicken with skin	No	75 (78.1)	161 (86.1)	1		
	≤1	9 (9.4)	13 (7)	1.4 (0.6–3.6)	0.38	0.04*
	2–4	9 (9.4)	10 (5.3)	1.9 (0.7–4.9)	0.17	<0.001*
	≥4	3 (3.1)	3 (1.6)	2.1 (0.4–10.8)	0.35	0.001*
Weekly consumption of Skinless chicken	No	12 (12.5)	43 (23)	1		
	≤1	30 (31.3)	46 (24.6)	2.3 (1.06–5.1)	0.03*	0.06
	2–4	39 (40.6)	71 (38)	1.9 (0.9–4.1)	0.07	0.99
	≥4	15 (15.6)	27 (14.4)	1.9 (0.8–4.8)	0.13	0.99
Weekly consumption of Fish	No	63 (65.6)	80 (42.8)	1		
	<1	32 (33.3)	92 (49.2)	0.4 (0.2–0.7)	0.002*	0.09
	1–3	1 (1)	15 (8)	0.08 (0.01–0.6)	0.01*	0.99
Weekly consumption of Tuna	No	54 (56.3)	92 (49.2)	1		
	<1	39 (40.6)	71 (38)	0.9 (0.5–1.5)	0.80	0.70
	1–3	3 (3.1)	24 (12.8)	0.2 (0.06–0.7)	0.01*	0.37
Weekly consumption of Hamburger	No	57 (59.4)	123 (65.8)	1		
	<1	30 (31.3)	54 (28.9)	1.1 (0.6–2.06)	0.51	0.30
	1–3	9 (9.4)	10 (5.3)	1.9 (0.7–5.04)	0.17	0.12
Weekly consumption of Sausages	No	61 (68.8)	122 (62.6)	1		
	<1	12 (12.5)	51 (27.3)	0.4 (0.2–0.8)	0.01*	0.26
	1–2	17 (17.7)	13 (7)	2.3 (1.06–5.07)	0.03*	0.03*
	>2	6 (3.2)	1 (1)	1.5 (0.6–3.5)	0.20	0.01*

*Significant at 95% confidence level.
[a]*P*-value without adjusted variables.
[b]*P*-value adjusted by race, socio-economic status, and tobacco consumption.

higher levels of HCA (27). Heterocyclic covalently bind and damage DNA in cultured human tissue (28).

In this study, the use of lamb meat had no significant association with the risk of EC, although a few studies reported that meat consumption increases the risk of EC. It can be caused by the method of cooking meat. Cooking methods such as grilled and fried meat are rich source of HCA and play an important role in the etiology of EC.

This study also showed no significant association between the consumption of fish and the risk of EC in multivariate logistic regression. However, some studies show that fish intake may increase the risk of cancer, such as breast cancer (29). In the present study, in univariate logistic regression analysis there was an inverse relationship between the consumption of fish and tuna with the risk of EC, so that fish consumption has a preventable role in EC. However, other studies had not shown association between fish consumption and cancer (30). Fish contains high amounts of n-3 long- chain PUFA which are suggested to hinder carcinogenesis. There are plausible mechanisms for a protective effect of n-3 long-chain PUFA on cancer risk, Including production of eicosanoids, and inhibition of cyclo-oxygenase-2, inhibition of mutation and increased of cell apoptosis (31,32). In this study, the average meat consumption was higher in Turkmen and because the race has shown a significant association with the risk of EC, we can be concluded that higher red meat consumption and cooking methods in these groups cause increase the risk of cancer. Other studies had shown different association between meat consumption and cancer in areas with different races (33).

In this study we had some limitations. We only evaluated the meat intake. We also use hospital controls that may potentially be related to their diet. We propose that in the future, the risk of EC should be studied in a population-based study and reviewed by all food groups.

Conclusion

The results of this study showed that consumption of red meat, chicken with skin, sausages, would increase the risk of EC. Fish had preventive role in cancer and since other studies had proven reducing risk of EC with consumption of vegetables and fruits; We recommended raise awareness through education with the help of the media to less consumption of red meat

and using green leafy vegetables, fruits, legumes, fish oil, which contains antioxidants, flavonoids, folic acid, phytosterols, vitamins A, E, C, and had anti-cancer properties.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

Author Contribution

Seyed-Javad Pournaghi: Study concept and design. Farhad Barazandeh Noveyri: Study concept and design. Hadi Mohammad Doust: Study concept and design. Ali Ahmadi: Statistical analysis. Andishe Hamedi: Study supervision, data analysis, interpretation of the data and revise manuscript. Jamileh Rahimi: Data gathering. Mahbobe Ghasemi: Data gathering. Hoda Hamidi: Data gathering. Maryam Gholamalizadeh: Data analysis. Saeid Doaei: Data analysis. Hossein Lashkardoost: Study supervision, data gathering, data analysis and interpretation of the data. Also revise manuscript.

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