

RESEARCH COMMUNICATION

Hormonal and Reproductive Factors and Risk of Esophageal Cancer in Chinese Postmenopausal Women: a Case-control Study

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Abstract

Aim: Since any relationship between hormonal and reproductive factors and risk of esophageal cancer is unclear, we investigated this question in Shandong province of China. **Methods:** A hospital-based 1:1 matched case-control study was conducted from January 2008 to November 2010, with face to face interviews conducted for 132 cases and 132 controls. All cases recruited in this study were confirmed by endoscopy and histological examination. Controls were first-visit outpatients who visited the same hospital during the same period and were confirmed to have no malignancy. Conditional logistic regression analysis was employed to calculate risk of potential factors. **Results:** Esophageal cancer positive women had a higher prevalence of reflux, smoking status, lower BMI and less education than health controls ($p < 0.05$). Women whose age of periods ended above 50 years and breastfed for more than 12 months had lower risk of esophageal cancer, with ORs (95% CI) of 0.42 (0.20-0.89) and 0.46 (0.21-0.98). Sensitivity analysis for the histological types of esophageal cancer showed no great difference between adenocarcinoma and squamous cell carcinoma. **Conclusion:** In summary, our findings suggest an inverse association between later age of menopause and duration of breastfeeding and risk of esophageal cancer. However, many reproductive and sex hormonal factors did not seem to be associated with esophageal cancer, supporting the need to further evaluate reproductive factors in prospective studies.

Keywords: Esophageal cancer - hormonal factors - reproductive factors - case-control study - China

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Introduction

Esophageal cancer is the sixth most common cancer worldwide in 2002 (Blount et al., 2007). In China overall, esophageal cancer ranks fourth in morbidity and it is estimated that almost half of the esophageal cancer cases in the world are occurred in China (IARC, 2011). Esophageal cancer has becoming an important public health problem in China.

Esophageal cancer has two main histological types, squamous cell carcinoma (ESCC) and adenocarcinoma (AC). ESCC is the dominant histological type both in Western and Asian countries (Engel et al., 2003). The overall incidence of esophageal cancer is on the rise, and this increase over the past two decades coincides with a change in the histological types and location (Vizcaino et al., 2001). Such inconsistent secular trends of histological types of esophageal cancer suggested the different etiology by histological type, and previous epidemiological studies have supported this hypothesis.

One interesting observation in the incidence of esophageal cancer is the sex discrepancies, which is an as yet unexplained feature of esophageal cancer. In Western countries, the incidence of esophageal cancer has a male

to female ratio of up to 6:1 (Parkin et al., 2005). In China, the male to female ratio of esophageal cancer is about 2:1 (Parkin et al., 2005). The strong male predominance is also age-related and differs by histological types, but could not be explained by gender-related differences in known risk factors or protective factors. The gender-associated difference in incidence rate may be attributable to an as yet unidentified protective factor in women, such as female sex hormones effects.

However, few studies have investigated the association between reproductive factors and risk of esophageal cancer, and finding of previous studies is conflicting. A previous study from UK reported a dose-dependent association was found between duration of breastfeeding and risk of esophageal cancer (Lindblad et al., 2006). Another population-based study suggested pre-menopausal was positive association with risk of esophageal cancer (Nilsson et al., 2003). However, a Swedish case-control study reported no evidence of an association between childbearing and esophageal adenocarcinoma (Lagergren and Jansson, 2005). A recent case-control study from China reported giving birth at later age attributed to increased 102% in esophageal cancer risk (Chen et al., 2011). Another recent systematic review suggested that

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breastfeeding was associated with a decreased risk of esophageal cancer (Cronin-Fenton et al., 2010).

Although there is several studies on the effect of sex hormone on esophageal cancer in women, most of the studies were conducted in western countries and the small sample size hampered an conclusive result by a low statistical power. We therefore conducted an 1:1 matched case-control study in Dezhou of China to investigate whether reproductive factors were related to the risk of female esophageal cancer.

Materials and Methods

A hospital-based case-control study has been carried out in the People's Hospital of Dezhou of Shandong province from the January 2008 to November 2010. All located female cases with newly diagnosed primary esophageal cancer between January 2008 to November 2010 were included in our study, and a face to face interview was conducted for them within two months after diagnosis. All cases recruited in this study were confirmed by endoscope and histological examination. A total of 137 patients aged 37-75 years were included in our study, all cases were interviewed with the participation rate of 100%. Hospital-based controls were individually matched to cases by gender and age (± 5 years). Controls were first-visit outpatients who visited the People's Hospital of Dezhou during the same period and were confirmed to have no malignancy, digestive diseases, chronic diseases and also no prior history of malignancy. Ratio of cases to controls was 1:1. Totally, we had 137 controls who were non-cancer or cancer-free subjects. Informed consents were obtained from patients and controls.

A self-administered structured questionnaire was used in our study, consisting 67 items. Information were collected about demographic (age, sex and family history of cancer) and clinical characteristics (histopathology, tumor location and lymph nodes status), tobacco usage, smoking, alcohol-drinking habits and dietary habits (including 45 foods/food groups), cardinal symptoms of gastroesophageal reflux, hormonal and reproductive factors. Completed questionnaires were obtained from 132 cases and 132 controls. Cancer patients were asked to refer about habits 5 years before diagnosis.

Statistical analysis was performed by using Stata version 8 (Stata, College Station, TX). Chi-square test or t test were used to analyze the differences of demographic and potential confounding factors between cases and controls. Conditional logistic regression analysis was employed to calculate odds ratios (ORs) and their 95% confidence intervals (CIs) for exposure variables. The association between exposure variables and risk of esophageal cancer was further examined after adjusting for potential confounders using multivariate logistic regression models. Potential confounding factors included age (categorized into three groups, <45, 45-55, >55 years), tobacco smoking status (former, never, ever over lifetime), alcohol consumption (former, never, ever over lifetime), education (years of education), history of reflux (never or ever, and assessed at 5 years before diagnosis).

The hormonal and reproductive factors included

Table 1. Characteristics of Controls and Esophageal Cancer Cases

Variables		Controls	Cases	P value
Age (years)	<45	47 (36)	39 (30)	>0.05
	45-55	52 (39)	61 (46)	
	>55	33 (25)	32 (24)	
Education (years)	<9	107 (82)	73 (55)	<0.001
	≥ 9	25 (19)	59 (45)	
History of reflux	No	98 (74)	119 (90)	0.001
	Yes	34 (26)	13 (10)	
Body mass index	<18	28 (21)	41 (31)	0.043
	18-25	29 (22)	36 (27)	
	>25	75 (75)	55 (42)	
Smoking status	Former	0 (0)	2 (2)	0.036
	Never	122 (92)	109 (83)	
	Ever	10 (8)	21 (16)	
Alcohol status	Former	4 (3)	6 (5)	0.72
	Never	91 (69)	86 (49)	
	Ever	37 (28)	40 (42)	

number of children born and age at menarche and menopause (cut-off points were defined based on biological consideration), history of pregnancy, breastfeeding among women who had a live birth and spontaneous abortion as well as hormone replacement therapy. Also we analyzed the risk differences taking into account the two main histological types.

Results

Characteristics of the 132 esophageal cancer female cases and 132 female control were included in Table 1. The mean ages of cases and controls were 57.2 ± 7.4 and 56.8 ± 6.6 years, respectively. There was no significant difference in age between cases and controls ($p=0.35$). Cases were significantly less educated than controls ($p<0.05$). Compared to the control group, the case group had a higher prevalence of reflux and smoking status as well as a lower BMI ($p<0.05$). But there were no significant differences between cases and controls in alcohol status ($p>0.05$).

The relation between esophageal cancer risk and selected on hormonal and reproductive factors was presented in Table 2. The OR was significantly lower for women whose age of periods ended above 50 years (OR=0.42, 95%CI=0.20-0.89). Women who breastfed for more than 12 months were at a 54% decreased risk of developing esophageal cancer (0.46, 95% CI=0.21-0.98). No association was observed with age at menarche, ever pregnant, number of deliveries, age at first birth, spontaneous abortion and hormone replacement therapy. But the risk of esophageal cancer reduced with the age of periods ended and duration of breastfeeding, and increased with the age at first birth.

After further stratified analysis for the histological type of esophageal cancer. The women whose age of periods ended above 50 years decrease the cancer risk in both ESCC and AC, and who breastfed for more than 12 months demonstrated a significant inverse association with AC risk. However, the results for this parameter showed there was no great difference among the various histological types.

Table 2. Association between Reproductive Factors and Risk of Esophageal Cancer

Variables	All types of EC		ESCC (no=88)		AC (no=44)	
	Control/Case	OR ¹ (95% CIs)	Control/Case	OR ¹ (95% CIs)	Control/Case	OR ¹ (95% CIs)
Age of menarche (years)	≤13	62/64 -	62/43 -	62/21 -		
	>13	70/68 0.97(0.47-1.68)	70/45 0.94(0.54-1.67)	70/23 1.02(0.51-2.23)		
Age of menopause (years)	>50	47/35 -	47/23 -	47/12 -		
	45-50	23/38 1.65(0.89-3.55)	23/28 2.16(1.14-4.78)	23/10 1.73(0.66-5.34)		
	<45	21/37 2.03(1.07-4.76)	21/24 2.27(1.03-4.97)	21/13 2.57(1.08-7.10)		
	Not	41/22 0.78(0.57-1.65)	41/13 0.69(0.30-1.63)	41/9 0.90(0.45-2.76)		
Ever pregnant	No	2/3 -	2/2 -	2/1 -		
	Yes	130/129 0.66(0.54-5.88)	120/86 0.75(0.13-10.79)	120/43 0.79(0.09-45.8)		
Number of children	0	2/3 -	2/3 -	2/0 -		
	1-2	103/96 0.62(0.05-5.56)	103/62 0.56(0.08-3.91)	103/34 -		
	≥3	27/33 0.81(0.06-7.68)	27/23 0.62(0.09-4.54)	27/10 -		
Age at first birth	<23	27/22 -	27/16 -	27/6 -		
	23-26	74/65 1.08(0.53-2.19)	74/47 1.09(0.51-2.45)	74/18 1.12(0.41-4.12)		
	>26	31/45 1.65(0.72-3.65)	31/25 1.42(0.60-3.46)	31/20 2.95(0.97-11.1)		
Spontaneous abortion	No	116/109 -	116/69 -	116/40 -		
	Yes	16/23 1.50(0.75-3.34)	16/19 2.15(0.94-4.67)	16/4 3.18(0.67-12.9)		
Breastfeeding among women who had a live birth						
Had children, never breastfed						
		18/29 -	18/15 -	18/14 -		
	Breastfed ≤6 months	30/37 0.73(0.29-1.66)	30/23 0.87(0.42-2.53)	30/14 0.79(0.35-2.01)		
	Breastfed 7-12 months	43/40 0.64(0.31-1.38)	43/28 0.82(0.34-2.05)	43/12 0.42(0.19-1.34)		
	Breastfed >12 months	41/36 0.46 (0.21-0.98)	41/22 0.71(0.27-1.70)	41/14 0.40(0.13-0.92)		
Hormone replacement therapy	Never	81/85 -	81/56 -	81/29 -		
	Ever	51/47 0.78(0.47-1.35)	51/32 0.94(0.53-1.70)	51/15 0.88(0.42-1.79)		

¹Adjusted for sex, age, history of reflux, BMI, smoking and drinking status

Discussion

The present study explored the hormonal and reproductive factors on esophageal cancer risk. This study suggested that late menopause was reported to be a protective for esophageal cancer. A tendency for reduction in esophageal cancer was observed in women who duration of breastfeeding, and an increased tendency was found in the age at first birth, but these trends were not statistically significant. Women who had a longer duration of breastfeeding appeared an inverse association with AC. This study was partially consistent with previous studies on esophageal cancer risks with respect to reproductive factors.

Late menopause was reported to be a protective factors in our study. Previous studies mentioned no effect of late menopause on esophageal cancer risk (Cronin-Fenton et al., 2010 ; Chen et al., 2011). We considered the late menopause is dependent on the growth and development of organs as well as body fat, indicating the age at menopause is affected by insufficient nutrition. Most of esophageal cancer women were sourced from rural areas, and the insufficient nutrition status might be a risk factors of esophageal cancer, and a healthy diet has been reported to decrease the incidence of this cancer.

We also found a reduced risk of esophageal cancer is associated with breastfeeding. Previous studies suggested a protective effect regarding cancers of the stomach, pancreas and gallbladder(Inoue et al., 2002; Heuch and Kvale, 2003; Heuch et al., 2008). The reasons for a reduced risk of esophageal cancer among women with a longer history of breastfeeding may be attributable to higher weight gain after pregnancy in women who did not breastfeed (Cheng et al., 2000). Another explanation

is similar to reasons of hormone related cancer, such as breast, endometrial and ovary. A high frequency of estrogen receptor expression has been reported in esophageal cancer (Utsumi et al., 1989; Akgun et al., 2002; Tiffin et al., 2003). Estrogen receptor expression breast cancer seem to have a better prognosis if they express the anti-apoptotic protein, bcl-2. Similarly, a loss of bcl-2 expression in esophageal cancer may have tumor progression and poorer survival (Raouf et al., 2003). Oxytocin, a hormone associated with breastfeeding, can regulate tumor growth via activation of the oxytocin receptor. Both oxytocin and its receptor have shown expression throughout the gastrointestinal tract, although their functions in the tract are not known (Monstein et al., 2004). The relatively transient depletion of estrogen and progesterone and high level of prolactin and oxytocin during breastfeeding are unlikely to have a direct impact on esophageal cancer development later in life (Battin et al., 1985). However, lactation may cause long-term modification of endogenous hormones or their receptors, increase prolactin and oxytocin and decrease a woman's cumulative exposure to oestrogen, and in this way decrease the risk of esophageal cancer. The androgen receptor has been shown to be expressed in esophageal cancer cells (Tihan et al., 2001). Our result is in line with a previous pooled analysis study(Cronin-Fenton et al., 2010).

Our study has several limitation which should be considered. First, there are many other risk factors of esophageal cancer which we did not considered, such as salted food, hot food, and other lifestyle habits, these would induce information bias, but we have collected the major risk factors and adjusted in our analysis. Second, the number of cases is limited, but the incidence of esophageal cancer in women is low, similarly, other studies also have

such problems. The limited cases could decrease the statistical power, and further study should increase the number of controls to increase the study power. Third, the hospital-based control may induce information bias, but our controls were selected from those who came to hospitals for routine health examination, and it could better represent the general population.

In summary, our findings suggest an inverse association between later age of periods ended and duration of breastfeeding and risk of esophageal cancer. But many reproductive and sex hormonal factors did not seem to be associated with esophageal cancer, supports the need to further evaluate the reproductive factors in prospective studies.

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