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## Study on the Dietary Factors of Esophageal Cancer

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### 1. Introduction

Esophageal Cancer (EC) is among upper digestive tract cancers and mainly prevalent in developing and underdeveloped countries. There are about 460,000 new cases of EC annually (World Cancer Research Fund & American Institute for Cancer Research [WRCF], 2007). The etiology of EC is complex, including heredity, environment and food factors, etc. The scientific community is convinced that both genetic and environmental factors play important role in EC's carcinogenesis. Although, inherited high susceptibility to EC accounts for part proportion of cases, exogenous exposures are also important for causing this disease. A number of studies have suggested that dietary factors are significant to the development of EC (De Stefani et al., 2006; Engel et al., 2003; Hung et al., 2004). And there is evidence that different varieties of food and nutrients could play a role in protecting against this disease (Chen et al., 2002; Liaw et al., 2003). In this chapter, evidence of food and nutrients on EC has been collected, and provide advices for the prevention of EC.

### 2. Meta-analysis of nutrients and EC

Meta-analysis has been a useful tool for providing combine quantitatively the evidence from different studies on specific research questions (Tatsionia & Ioannidis, 2008). In order to summarize the relationship between nutrients and risk of EC, we did meta-analysis of the relationship between dietary factors and occurrence of EC.

#### 2.1 Vegetables and fruits

Vegetables and fruits are sources of a wide variety of micronutrients and are rich in antioxidant substances, among them,  $\beta$ -carotene and vitamin C have been shown to play protective role in the occurrence and development of EC (Michels et al., 2005; Terry et al., 2000). As we all known, vegetables and fruits also contain dietary fiber and other bioactive compounds, which are termed as phytochemicals (Soler et al., 2001). They can play

important role in the functions of the plant, such as providing flavour, color, or supporting protection (WCRF, 2007). The phytochemicals include many varieties such as flavonoids, isoflavones, glucosinolates and so on, but they are not essential in the human diet (WCRF, 2007). Many researches either in humans or in laboratory experiments have shown that most of the bioactive compounds have potentially beneficial health effects when they are included in diets (Franceschi et al., 2000; Freedman et al., 2007). However, the bioavailability of these compounds is variable and their ultimate health effects are needed to study further.

The average vegetable consumption (not including vegetable oil) of global population is 2.6 percent of total daily energy intake (Food and Agriculture Organization of the United Nations, [FAOSTAT], 2006). It is generally high in North Africa, the Middle East, parts of Asia, the USA and Cuba, and in southern Europe. The global average for fruit consumption (based on availability) is 2.7 percent of total daily energy intake (FAOSTAT, 2006). Fruit consumption is generally higher than vegetable consumption, but it shows a great variability in different areas.

The case-control or cohort studies from 1995 to 2011 on vegetables, fruits and EC have been collected with searching tools such as Web of Science, PubMed. The keywords were “esophageal cancer”, “diet”, “nutrients”, “vegetables” and “fruit”, and selected odds ratio (OR) as effect index. All the relevant studies have been identified. The heterogeneity test, a fixed effect model or random effect model has been selected to calculate the combined OR and OR 95% confidence interval (95%CI). The software of Stata 11.0 has been used for the meta-analysis.

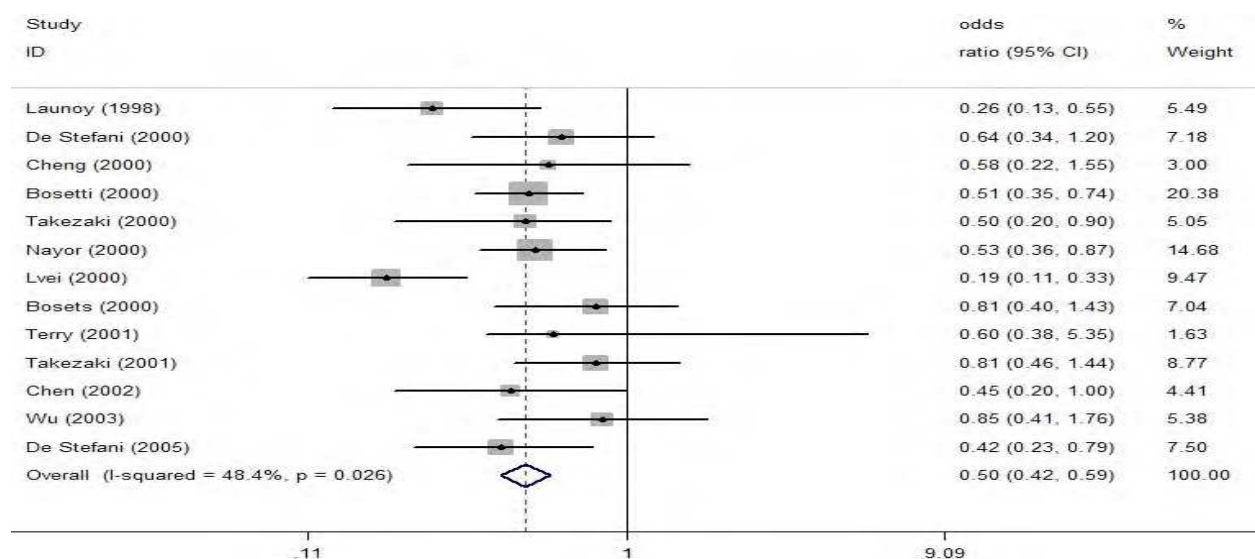


Fig. 1. Forest plot of vegetables and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by highest versus lowest exposure category of vegetables intake.

23 case-control studies and only three cohort studies (Fan et al., 2008; Tran et al., 2005; Zheng et al., 1995) have investigated relation between vegetables and EC, among them, 16 case-control studies have shown decreased risk with increased vegetables intake, which were statistically significant. Only one case-control study has shown an increased risk

(OR=1.54, OR 95%CI: 1.10-2.16) (Takezaki et al., 2001), and six case-control studies were non-significant difference (Bosetti et al., 2000; Chen et al., 2002; Cheng et al., 2000; Zhang et al., 1997; Wu et al., 2003; Yang et al., 2005). The data of studies have suggested an association with reduced risk when increased vegetables intake. According to the different exposures which have been collected from the studies, the OR has been analyzed for two parts, one was the highest versus lowest exposure category, and the other was consumption frequently versus consumption occasionally or less category. The combined OR and OR 95%CI for case-control studies of vegetables and EC were 0.50, 0.42-0.59 (figures 1) and 0.66, 0.61-0.72 (figures 2). The evidence of cohort studies for vegetables and EC has not been enough. Among the three cohort studies, one of which has described association between vegetables and esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EAC) respectively. The relative risk (RR) and RR 95%CI for ESCC were 0.57, 0.28-1.18 and they were 0.92, 0.57-1.50 for EAC, but both were non-significant statistically (Freedman et al., 2007). The other two cohort studies were also non-significant difference (Fan et al., 2008; Tran et al., 2005). All the studies have been adjusted for confounding factors.

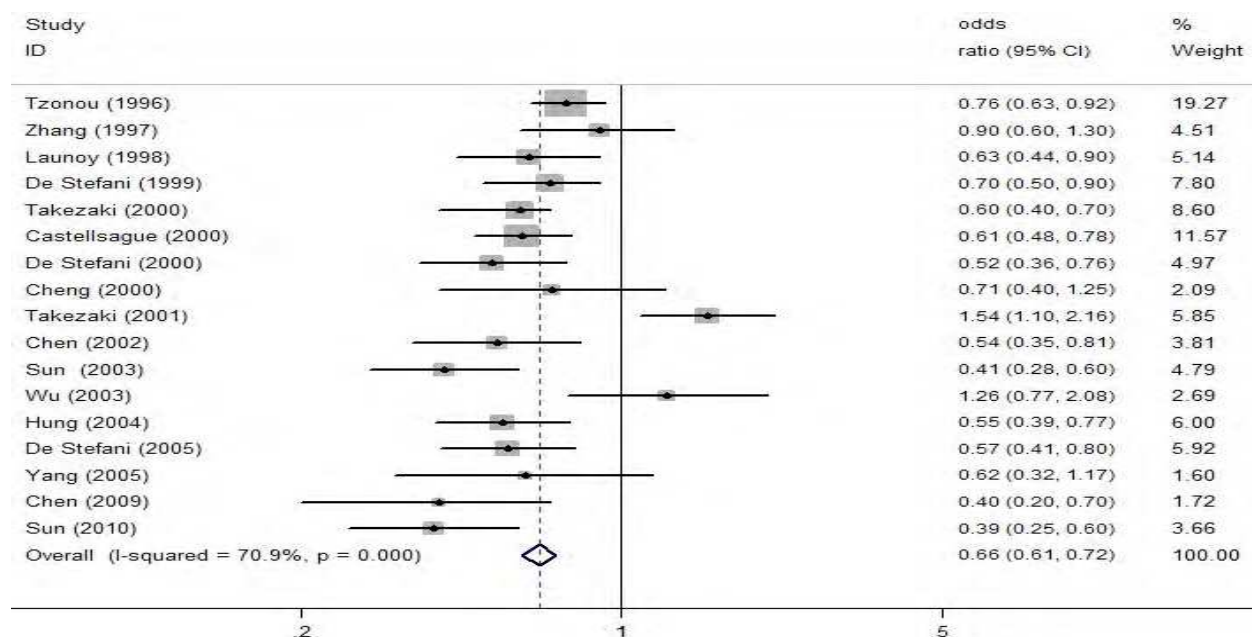


Fig. 2. Forest plot of total vegetables and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by eating frequently versus eating occasionally or less category, the individuals who eat vegetables  $\geq 1$  time/d versus those who eat  $< 1$  time/ d.

24 case-control studies have investigated association between fruits and EC, 14 of which have shown relationship between fresh fruits consumption and reduced risk of EC (Bosetti et al., 2000; Castellsague et al., 2000; Chen et al., 2009; Cheng et al., 2000; De Stefani et al., 1999; De Stefani et al., 2000; De Stefani et al., 2005; Hung et al., 2004; Sun et al., 2003; Takezaki et al., 2000; Terry et al., 2001; Wang et al., 1999; Wu et al., 2003; Yang et al., 2005), with the other 10 studies reporting results of non-significant difference (Gao et al., 1999; Launoy et al., 1998; Nayar et al., 2000; Phukan et al., 2001; Sharp et al., 2001; Takezaki et al., 2000; Takezaki et al., 2001; Tzonou et al., 1996; Wu et al., 2003; Zhang et al., 1997). Four

cohort studies have shown data on the fresh fruits and EC, RR of the two studies have suggested that fresh fruits intake strongly associated with decreased risk of EC (Fan et al., 2008; Tran et al., 2005). Another one cohort study has shown no relationship between fruits and EC (Zheng et al., 1995). Also one study has found a significant inverse association between total fruits and vegetables intake and ESCC risk (RR: 0.78, 95%CI: 0.67-0.91), but not EAC risk (0.98, 0.90-1.08) (Freeman et al., 2007). The combined OR and OR 95%CI (highest versus lowest exposure category) of case-control studies for fruits and EC were 0.57, 0.49-0.66 (figure 3). And the combined OR and OR 95%CI (eating frequently versus eating occasionally or less category) of case-control studies for fruits and EC were 0.60, 0.55-0.66 (figure 4).

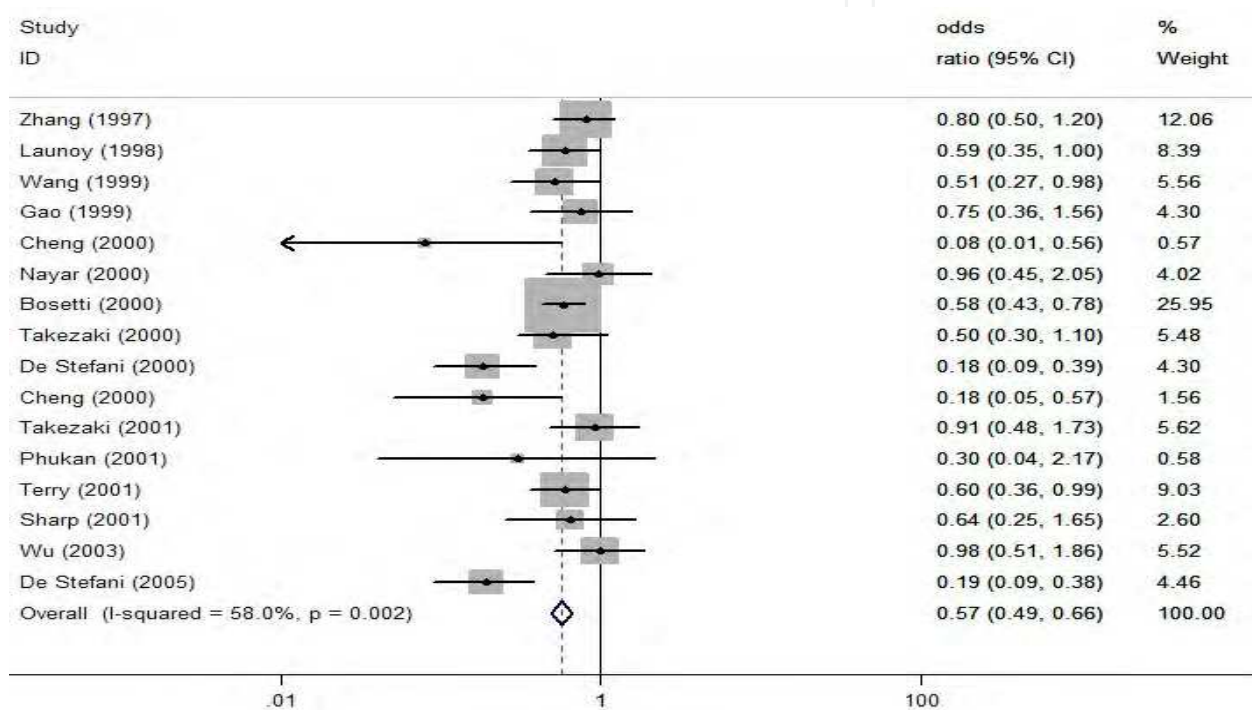


Fig. 3. Forest plot of fruit and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by highest versus against lowest exposure category of fruit intake.

Three case-control studies have investigated vegetables and fruits combined consumption and EC (De Stefani et al., 2000; De Stefani et al., 2005; Zhang et al., 1997). All the data of studies have suggested an association with reduced risk. The results of meta-analysis for the relationship between vegetables, fruits and EC have shown that they could probably protect people from EC.

## 2.2 Vitamin A

Vitamins are organic molecules, and classified as fat- or water-soluble, which are essential for metabolism but cannot be made in the body. Most vitamins must be supplied from the diet. Vitamin A is a fat-soluble vitamin and can only be digested, absorbed, and transported in conjunction with dietary fats. An important source of vitamin A is from plant foods such as green leafy vegetables and fruits that contain the retinol precursors known as carotenoids,

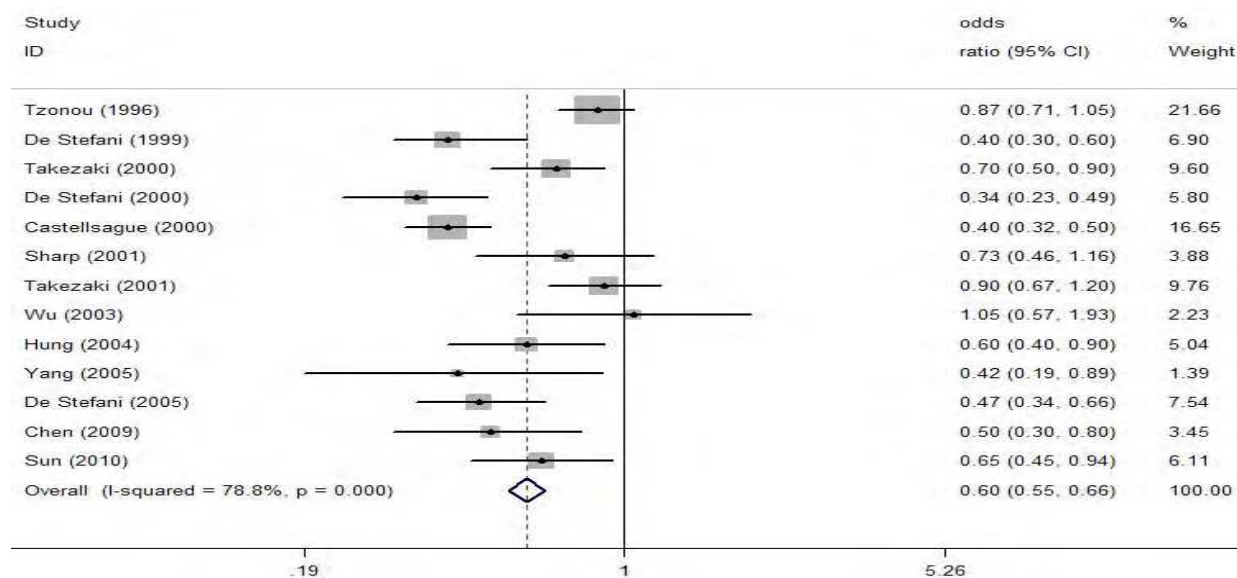


Fig. 4. Forest plot of total fruit and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by eating frequently versus eating occasionally or less category, the individuals who eat fruit  $\geq 1$  time/d versus those who eat  $< 1$  time/ d.

most importantly  $\beta$ -carotene, which can be converted by the body to retinol, and sometimes are called pro-vitamin A carotenoids. Other sources of vitamin A are from animal foods such as liver, milk and eggs, which can be used by the body directly (WCRE, 2007). Some studies have suggested that vitamin A could play a crucial role in protecting damaged epithelial cells against attack by carcinogens, and esophageal epithelial cells are more sensitive to the deficiency in vitamin A (Poulain et al., 2009).

The meta-analysis has been made respectively for relationship between vitamin A,  $\beta$ -carotene of diet and EC. The case-control or cohort studies from 1995 to 2011 on vitamin A and EC have been collected with searching tools such as Web of Science, PubMed. The keywords were "esophageal cancer", "diet", "nutrients", "vitamin A", "beta- carotene", and selected OR as effect index. Then the method of next step was the same as which has been used for vegetables and EC.

A total of eight case-control studies (Bollschweiler et al., 2002; Chen et al., 2002; De Stefani et al., 1999; Franceschi et al., 2000; Mayne et al., 2001; Terry et al., 2000; Tzonou et al., 1996; Zhang et al., 1997) and one eligible cohort study (Zheng et al., 1995) have investigated vitamin A, retinol and  $\beta$ -carotene of diet, also two cohort studies have investigated retinol and  $\beta$ -carotene in serum (Abnet et al., 2003; Nomura et al., 1997). The evidence for vitamin A and EC was limited; since there have been only three eligible studies before 2001 (De Stefani et al., 1999; Mayne et al., 2001; Tzonou et al., 1996). The combined OR and 95%CI for it were 0.66, 0.49-0.89 (figure 5). Five case-control studies have published data on the  $\beta$ -carotene of diet and EC, and only two eligible studies have shown decreased risk when comparing the highest intake group against the lowest of vitamin A intake. The combined OR and OR 95%CI of meta-analysis were 0.66, 0.54-0.81 (figure 6). A decreased risk associated with high retinol and  $\beta$ -carotene intake were also consistent findings in several studies on EC. The result of meta-analysis has suggested of food containing vitamin A may protect body against EC and need further study.

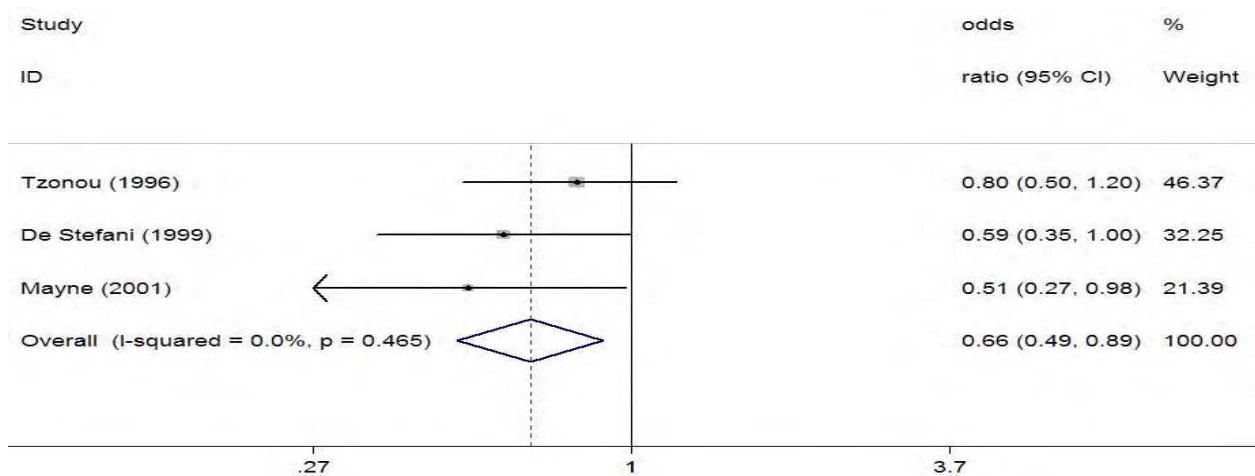


Fig. 5. Forest plot of total vitamin A and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by the 75th percentile versus the 25th percentile of vitamin A intake.

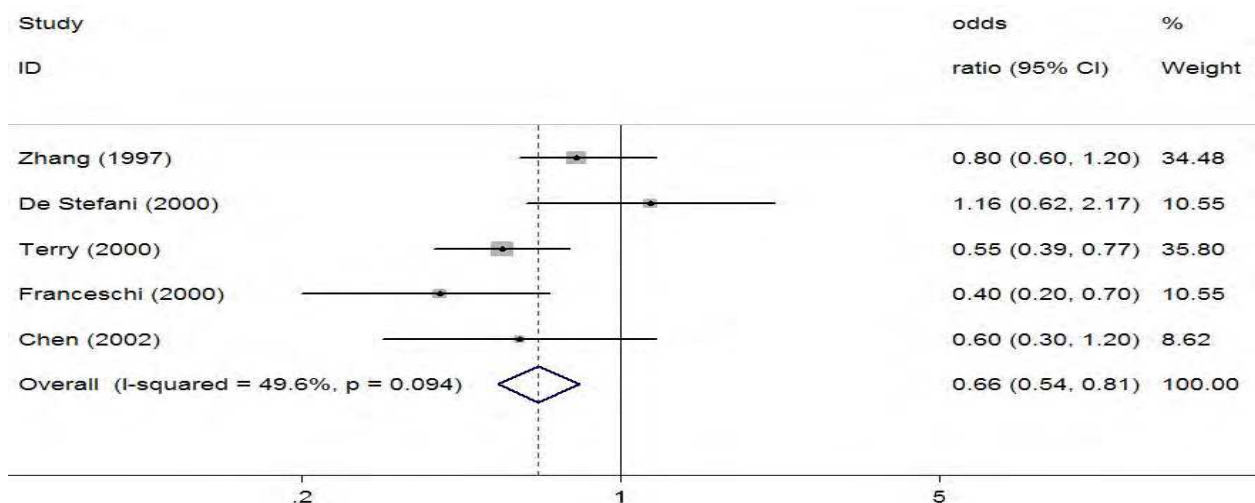


Fig. 6. Forest plot of  $\beta$ -carotene and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by highest versus lowest exposure category of  $\beta$ -carotene intake.

### 2.3 Folic acid

Folic acid is one of B vitamins which is water-soluble, and is equivalent of pteroylglutamic acid. The main sources of folic acid are lettuce, spinach and tangerine etc vegetables and fruits (WCRF, 2007). Folic acid is involved in a number of metabolic pathways, especially in the synthesis of purines and pyrimidines (Tan et al., 2005). A few studies have suggested that folic acid is important for DNA synthesis and methylation (Axumea et al., 2007; Kima et al., 2009). But limited evidence has supported high folic acid intake may reduce risks of EC overall.

The case-control or cohort studies from 1995 to 2011 on folic acid and EC also have been collected with searching tools such as Web of Science, PubMed. The keywords were "esophageal cancer", "diet", "nutrients", "folic acid", and selected OR as effect index. Then the method of next step was the same as which has been used for vegetables and EC.

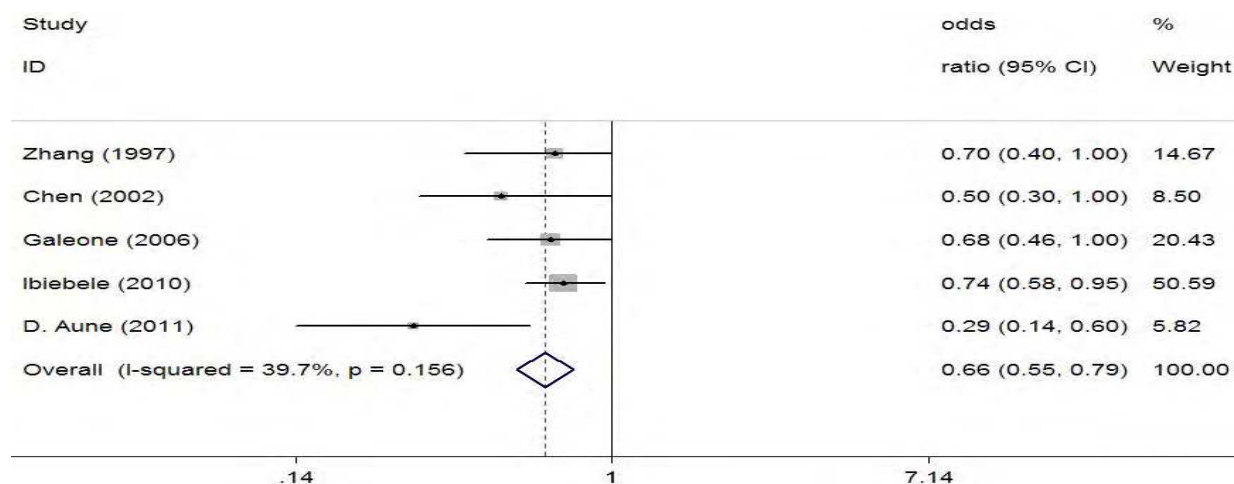


Fig. 7. Forest plot of folic acid and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by highest versus lowest exposure category of folic acid.

A total of eight case-control studies have evaluated the relationship between intake of folic acid from foods and supplements and risk of EC (Aune et al., 2011; Chen et al., 2002; De Stefani et al., 1999; Franceschi et al., 2000; Galeone et al., 2006; Ibiebele et al., 2010; Mayne et al., 2001; Zhang et al., 1997). Of which two case-control studies have reported that dietary folic acid could decrease risk of EC in the highest intake groups when compared to the lowest (Aune et al., 2011; Ibiebele et al., 2010). Only one eligible case-control study has analyzed thymidylate synthase genotype and serum folic acid concentration in patients with ESCC and controls (Tan et al., 2005). The data of meta-analysis have shown that the combined OR was 0.66, and 95%CI was 0.55-0.79 when analyzed the highest versus lowest exposure of folic acid and EC (figure 7). Our result has indicated that folic acid could protect individuals against EC, but still need collect data of further research in population.

## 2.4 Vitamin C

It is generally that plant foods are important sources of vitamin C. Non-starch vegetables and fruits are rich in vitamin C, which can be directly absorbed by the body. But vitamin C in the foods can be destroyed by heat or exposure to the air, or lost by leaching during cooking (WCRF, 2007). It is biologically demonstrated that vitamin C could protect against EC because it can trap free radicals and reactive oxygen molecules, protecting from lipid peroxidation, reducing nitrates, and stimulating the immune system (Odin, 1997). Moreover, it can recycle other antioxidant vitamins. Many studies have shown that vitamin C could inhibit formation of carcinogens and protect DNA from mutagenic attack (Hercberg et al., 1998). However, evidence supporting a specific mechanism in the esophagus is limited.

The case-control or cohort studies from 1995 to 2011 on vitamin C and EC have been collected with searching tools such as Web of Science, PubMed. The keywords were "esophageal cancer", "diet", "nutrients", "vitamin C", and selected OR as effect index. Then the method of next step was the same as which has been used for vegetables and EC.

Totally, ten case-control (Chen et al., 2002; De Stefani et al., 1999; De Stefani et al., 2000; Franceschi et al., 2000; Kubo et al., 2008; Launoy et al., 1998; Mayne et al., 2001; Terry et al.,



2000; Tzonou et al., 1996; Zhang et al., 1997) and one eligible cohort studies (Zheng et al., 1995) have investigated the relationship between vitamin C of diet and EC. Most of the researches except one (Zhang et al., 1997) have published that a strongly association between high intake of vitamin C and decreased risk of EC. The single eligible cohort study has reported a non-significant reduced risk for the highest intake groups when compared to the lowest after adjustment for smoking, with OR of 0.70 (95%CI: 0.30-1.70). The combined OR and 95%CI of the 75th percentile intake versus the 25th percentile of vitamin C intake were 0.57, 0.52-0.63 (figure 8). Another combined OR and 95%CI (highest versus lowest exposure category) were 0.66, 0.55-0.79 (figure 9). The results of meta-analysis have suggested vitamin C could probably have an effect of prevention of EC.

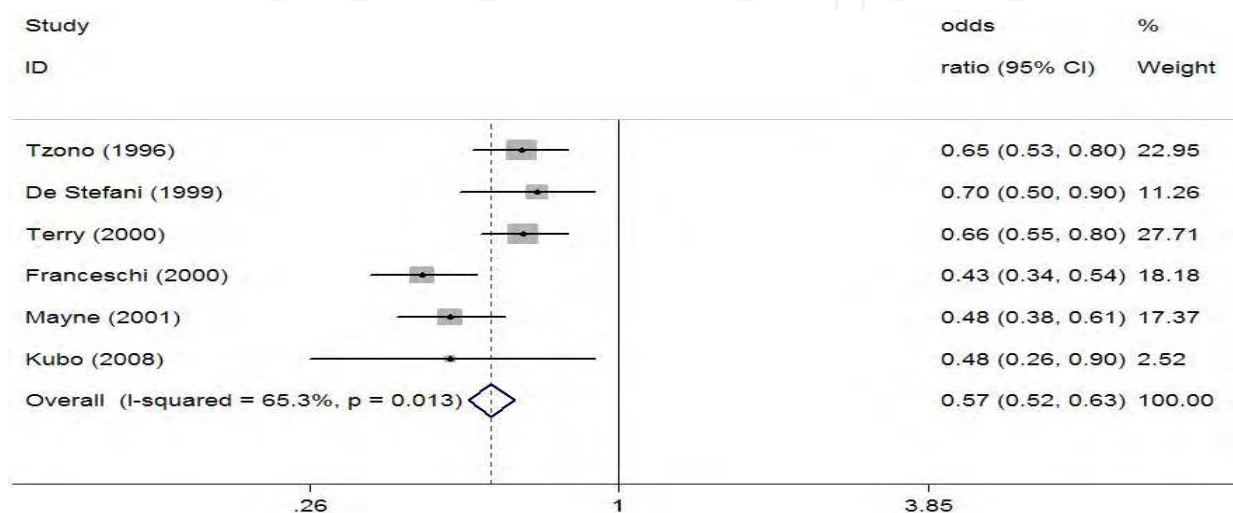


Fig. 8. Forest plot of total vitamin C and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by the 75th percentile versus the 25th percentile of vitamin C intake.

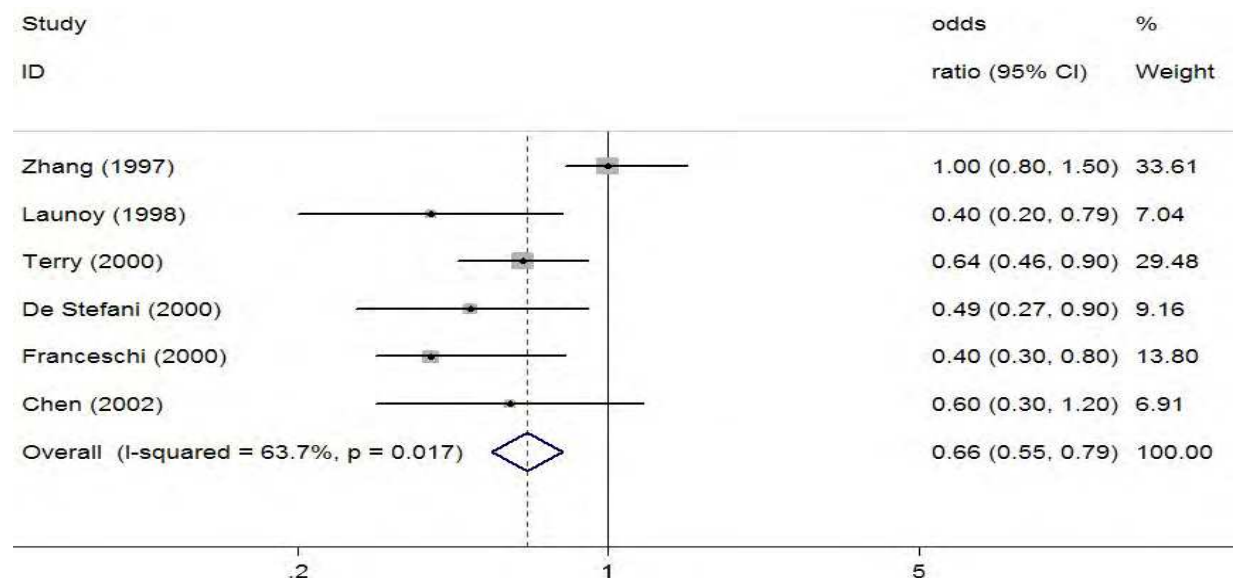


Fig. 9. Forest plot of vitamin C and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by highest versus lowest exposure category of vitamin C intake.

## 2.5 Vitamin D

Vitamin D is fat-soluble of vitamins, which is a sort of substances showing the biological activity of ergocalciferol (vitamin D<sub>2</sub>) and cholecalciferol (vitamin D<sub>3</sub>), and 1,25-(OH)<sub>2</sub>D<sub>3</sub> is the main active form of vitamin D (Reddy et al., 2006). The seafood and liver of animals are rich in vitamin D. Experimental researches have shown that 1,25-(OH)<sub>2</sub>D<sub>3</sub> could inhibit the proliferation of EC cell EC-9706, and it is important for prevention and treatment of EC (He et al., 2009). The anti-tumor mechanism of 1,25-(OH)<sub>2</sub>D<sub>3</sub> may be that it could primarily inhibit cycle progression of tumor cells, causing G<sub>1</sub> phase of tumor cells arrest, the cell number of S phase was decreased, and accumulation of G<sub>0</sub>/G<sub>1</sub> phase, so that inducing the differentiation and maturity of tumor cells (He et al., 2009). But there have been not enough evidence to demonstrate the association between vitamin D and EC. Only three eligible case-control studies have investigated the relationship between diet of vitamin D and EC (Franceschi et al., 2000; Launoy et al., 1998; Mayne et al., 2001). Among them, all the results have shown the decreased risk when appropriate intake of vitamin D, but two of which were non-significant difference.

## 2.6 Vitamin E

Vitamin E is a family of eight compounds collectively referred as tocopherols, of which alpha- and gamma-tocopherol are the most common. Vitamin E is a fat-soluble vitamin. The most important dietary sources of vitamin E are vegetable oils such as soya bean, corn, olive oils, sunflower, and palm. Nuts, sunflower seeds, and wheat germ also contain this vitamin. Vitamin E can act as antioxidants and free radical scavengers (WCRF, 2007). However, few studies have supported it has an anti-cancer effect of esophagus.

The case-control or cohort studies from 1995 to 2011 on vitamin E and EC also have been collected with searching tools such as Web of Science, PubMed. The keywords were "esophageal cancer", "diet", "nutrients", "vitamin E", and selected OR as effect index. Then the method of next step was the same as which has been used for vegetables and EC.

Nine case-control studies (Bollschweiler et al., 2002; Chen et al., 2002; De Stefani et al., 1999; De Stefani et al., 2000; Franceschi et al., 2000; Kubo et al., 2008; Launoy et al., 1998; Mayne et al., 2001; Zhang et al., 1997) and one cohort study (Zheng et al., 1995) have shown the relationship between dietary vitamin E and EC, and two cohort studies have investigated the role of serum vitamin E (Nomura et al., 1997; Taylor et al., 2003). Six case-control studies have reported decreased risk for the highest intake groups when compared to the lowest, which was statistically significant in four, the other studies have reported no effect on EC risk (figure 10). The cohort studies and most case-control studies have shown decreased risk with increased vitamin E intake, but case-control data about serum vitamin E were inconsistent. Both cohort studies have shown decreased risk for the highest level groups of vitamin E intake when compared to the lowest. The combined OR and OR 95%CI of the 75th percentile versus the 25th percentile of vitamin E intake were 0.53, 0.46-0.63 (figure 11).

## 2.7 Tea

Currently, tea, in the form of green, black or oolong tea, is the most widely consumed beverage in the world. The main active component of tea is polyphenol. In vitro and animal

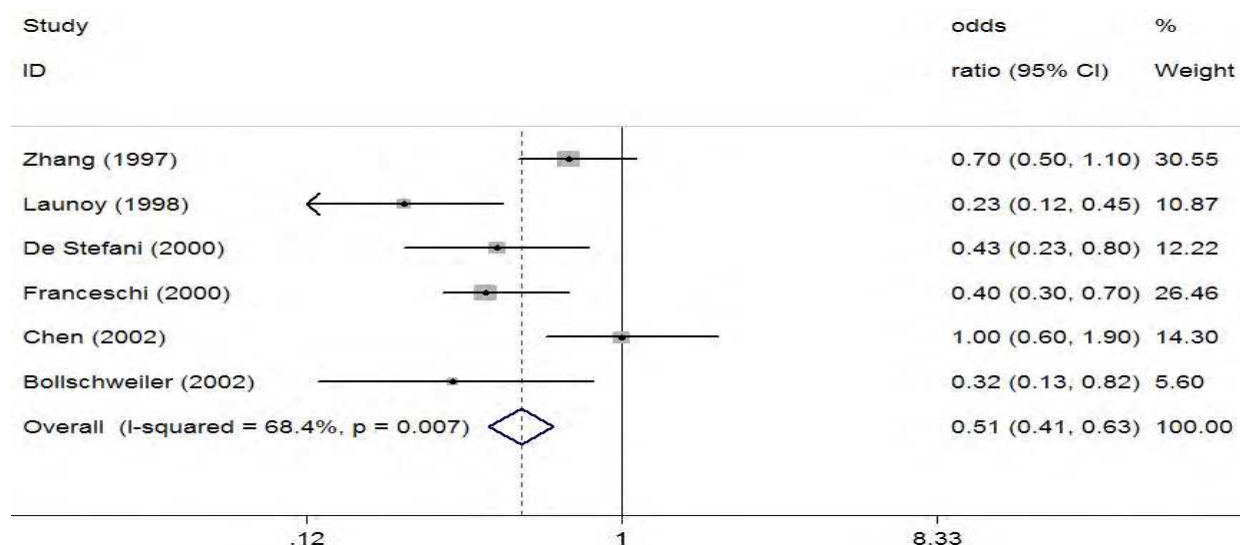


Fig. 10. Forest plot of vitamin E and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by highest versus lowest exposure category of vitamin E intake.

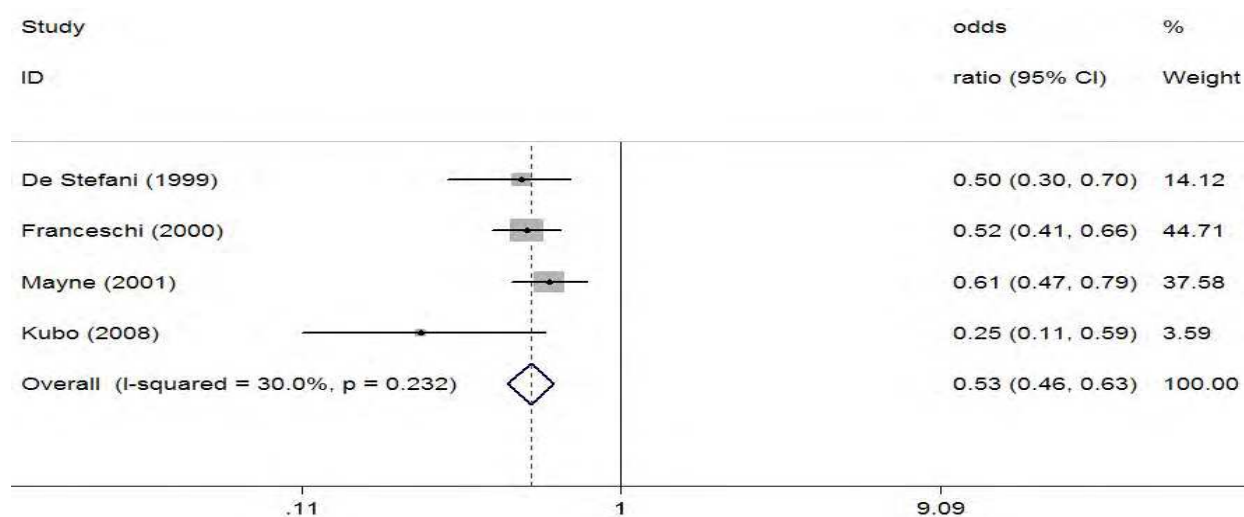


Fig. 11. Forest plot of total vitamin E and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by the 75th percentile versus the 25th percentile of vitamin E intake.

studies have provided strong evidence that polyphenol derived from tea may possess the bioactivity to affect the pathogenesis of different cancers (Khan & Mukhtar, 2007). The association between drinking different tea and risk of EC have been reported in several studies from different parts of the world (Castellsague et al., 2000; Ganesh et al., 2009; Ibiebele et al., 2010; Li et al., 2002). But for different kinds of tea, there has been still little evidence for an association between amount of use and EC risk. Moreover, the majority of studies have shown an increased risk of EC associated with drinking higher temperature tea which was statistically significant in most of them (Wang et al., 2007; Lin et al., 2010).

The case-control or cohort studies from 1995 to 2011 on tea and EC have been collected with searching tools such as Web of Science, PubMed, China National Knowledge Infrastructure.

The keywords were “esophageal cancer”, “tea”, “green tea”, “black tea”, “maté” and selected OR as effect index. Then the method of next step was the same as which has been used for vegetables and EC.

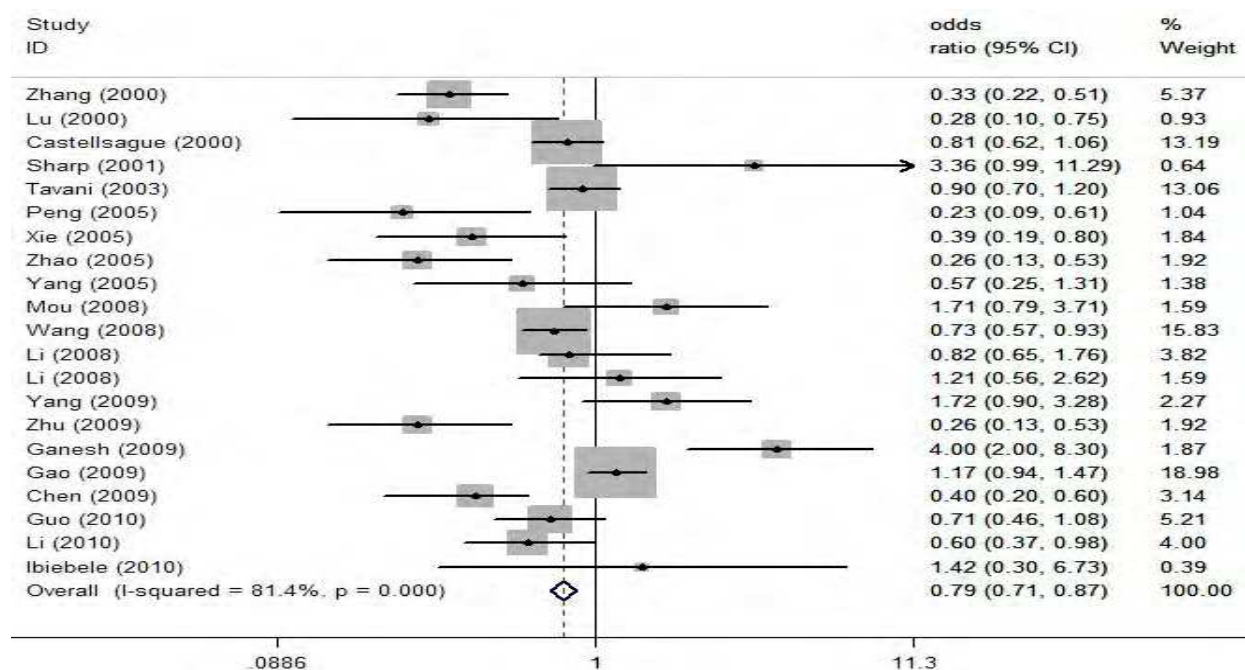


Fig. 12. Forest plot of tea and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by drinking frequently versus drinking occasionally or less category of tea.

A total of 21 case-control studies have published the tea and EC (figure 12). 14 studies have shown decreased EC risk when comparing drinking frequently against drinking occasionally or less category, nine of which the OR were statistically significant (Chen et al., 2009; Li et al., 2010; Lu et al., 2000; Peng et al., 2005; Wang et al., 2008; Xie et al., 2005; Zhang et al., 2000; Zhao et al., 2005; Zhu et al., 2009), but five studies were not statistically significant (Castellsague et al., 2000; Guo et al., 2010; Tavani et al., 2003; Yang et al., 2005; Li, 2008). Another six studies have suggested increased risk of EC with high tea drinking (Gao et al., 2009; Mou et al., 2008; Sharp et al., 2001; Ibiebele et al., 2010; Yang et al., 2009). However, only one eligible study has shown the OR for drinking tea and EC was 4.0, 95%CI was 2.0-8.3 in Indian population (Ganesh et al., 2009). The combined OR and OR 95%CI (drinking frequently versus drinking occasionally or less category) of case-control studies for EC were 0.786, 0.713-0.866. The results have suggested that drinking tea could probably protect body against EC.

### 2.7.1 Green tea

Green tea is favored in Japan and China, and majority of studies researched on the benefits of green tea were carried out in these countries because of the local customs. The processing of green tea is different from black tea. When producing green tea, freshly harvested leaves are steamed to prevent fermentation, yielding a dry, stable product (WCRF, 2007). Tea

polyphenols, which are known as catechins, usually account for 30-42% of the dry weight of green tea (Khan & Mukhtar, 2007).

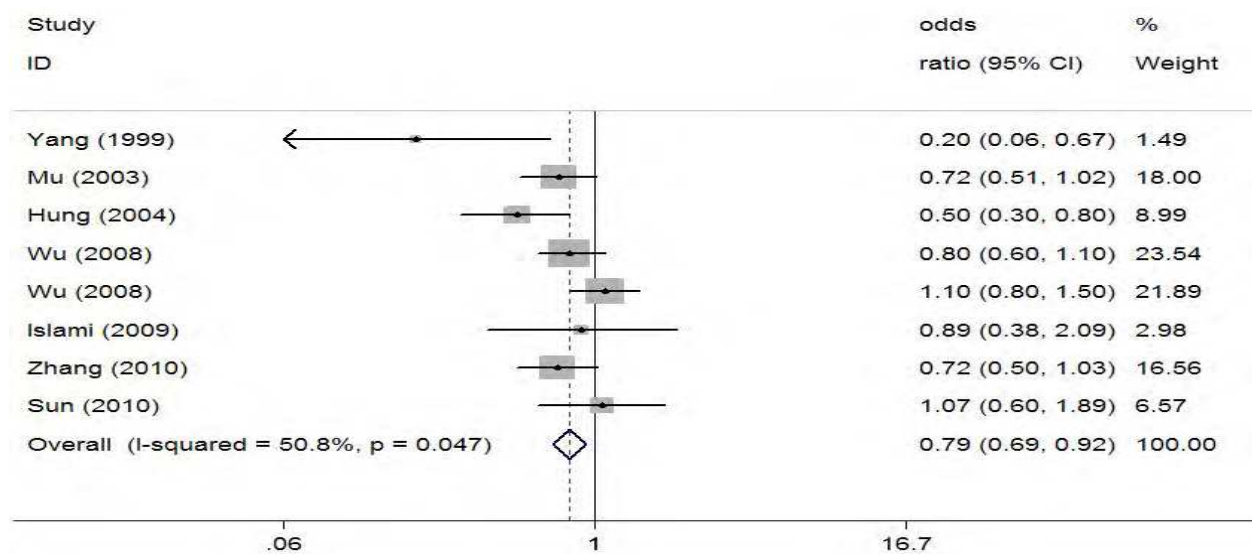


Fig. 13. Forest plot of green tea and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by drinking frequently versus drinking occasionally or less category of green tea.

Seven case-control studies have investigated the association between green tea and EC, and most of them from Chinese population, five studies have shown decreased risk when comparing the drinking great tea group against the non-drinking (Yang et al., 1999; Hung et al., 2004; Islami et al., 2009; Mu et al., 2003; Zhang et al., 2010), of which four were non-significant in statistics. However, two studies have shown that an inverse association between green tea and EC, with no difference in statistics (Sun et al., 2003; Wu et al., 2008). The combined OR and 95%CI of drinking frequently versus drinking occasionally or less category of green tea were 0.79, 0.69-0.92 (figure 13). The results of meta-analysis for green and EC have suggested it has the function for prevention of EC.

### 2.7.2 Black tea

The black tea composition depends on a technological process known as fermentation, in which about 75% of catechins contained in the tea leaves are crushed to promote enzymatic oxidation and subsequent condensation of tea polyphenols, leading to the formation of oligomeric polyphenols (theaflavins) and polymeric polyphenols (thearubigins) (WCRF, 2007). It is difficult to state a definitive composition for black tea, as it varies with different preparations. Four case-control studies have investigated the relationship between black tea and EC, and the results were not consistent, for two studies have shown increased risk with high drinking of black tea (Chen et al., 2009; Islami et al., 2009), the other two studies have suggested black tea was inversely associated with EC (Gao et al., 2009; Zhang et al., 2010), but all the studies were non-significant statistically (figure 14). The combined OR and 95%CI of drinking frequently versus drinking occasionally or less category of black tea were 1.07, 0.69-1.65. The evidence for black tea is limited and needs further study.

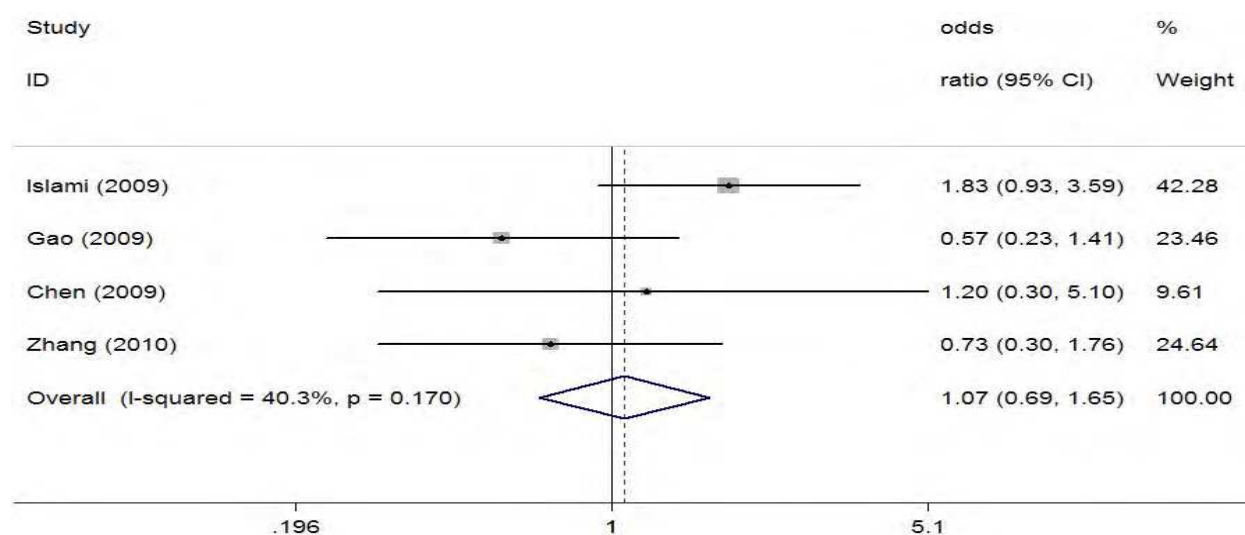


Fig. 14. Forest plot of black tea and EC, case-control study. The rhombus is stand for the combined OR, and the OR is calculated by drinking frequently versus drinking occasionally or less category of black tea.

### 2.7.3 Maté

Maté, a tea-like infusion of the herb *Ilex paraguariensis*, is particularly prevalent in southern America, Brazil and in Uruguay. And it is typically drunk scalding hot through a metal straw. This process of heat may damage esophagus (Castellsague et al., 2000). Repeated damage of this nature could lead to cancer of esophagus. Chemical carcinogenesis from constituents of maté has also been postulated.

For maté drinking, the number of studies was limited, but they consistently have shown that EC risk increased with both amount and temperature consumed, and these two were independent risk factors. Three case-control studies have investigated relationship between maté and EC (Castellsague et al., 2000; Sewram et al., 2003; Szymańska et al., 2010). All of them have suggested that an increased incidence of EC with higher maté consumption. Our meta-analysis of case-control data have shown OR was 1.796, 95%CI was 1.363-2.366. The results have shown that maté, an herbal infusion, is probably a cause of EC.

### 3. A case-control study on the relationship between dietary nutrients intake and EC in China

China is the high EC incidence and mortality country in the world, accounting for more than 50% of new cases in the world, each year about 250,000 cases of newly diagnosed EC, the incidence rate is 19.83/10<sup>5</sup> and mortality rate is 16.01/10<sup>5</sup> (Chen et al., 2008; Zhang et al., 2008). The incidence of EC has big regional difference. Chuzhou District, Huaian City, Jiangsu province, China, is a high-incidence area of EC with ESCC incidence over 98/10<sup>5</sup>, which is 7 times higher than the nation's average rate (13/10<sup>5</sup>) (Hu et al., 2002). Recent years, with the development of the economy, improvement of medical level and enhancement of people's awareness of preventing diseases, incidence of EC has been declining in some of the high-incidence areas in China (Yang et al., 2008), but it is still high in Chuzhou District, Huaian City. The risk factors of EC need to be studied further in this area.

### **3.1 Subjects and methods**

#### **3.1.1 Cases and controls**

In the EC high incidence area of Chuzhou District, Huaian City, Jiangsu Province, we have conducted a case-control study of dietary factors and risk of EC. A total of 207 EC cases with newly diagnosed as ESCC by the X-ray, endoscopic or pathological diagnosis in county and above county level hospitals from 2003 to 2008 were considered eligible for the study. The cases were drawn from the local cancer registered system.

Each case was matched within 5 years of age, same sex and nationality by two control subjects who were recruited from the same district. If the people do not want to attend the study, select again randomly, 414 controls were selected in total.

#### **3.1.2 Methods**

All the participants were interviewed to fill a structured questionnaire by trained investigators after obtaining written informed consent. The questionnaire included questions about sociodemographic characteristics, occupational history, dietary habits and a detailed food-frequency questionnaire (FFQ) on the intake of 120 food items one year before. Subjects were asked to report how many times they consumed 120 different foods per day, per week, per month or per year and how much per time. This FFQ was considered as representative of this area diet and allowed for the estimation of total energy and nutrients intakes. All data were entered by different persons on two computers using Epidata3.1 software. The total energy and nutrients intake have been calculated using Chinese Food Ingredients Table 2002 (Yang et al., 2002).

#### **3.1.3 Statistical analysis**

Single factor logistic analyses for intake of different food groups and interested nutrients were conducted using SPSS 13.0 software to determine differences between controls and cases. Then, unconditional logistic regression was used to calculate OR and corresponding 95%CI for EC compared with controls in relation to daily food group and nutrients intake.

### **3.2 Results**

#### **3.2.1 General status**

There were 207 EC cases and matched 414 controls who completed the FFQ after further exclusion of participants with implausible energy intake (<600Kcal/d or >5000Kcal/d). 112 pairs (one pair included one case and two controls) were males and 95 pairs were females. There was no significant difference ( $P>0.05$ ) between cases and controls in age, ethnicity, education level, marital status, etc., and all the cases and controls were farmers (Table 1).

#### **3.2.2 Dietary intakes of foods and nutrients**

The daily foods have been divided into 8 categories, 120 species. According to survey data of FFQ, all kinds of food daily intakes were calculated in Table 2 [if the variance of data was heterogeneity, the data were listed with the median (M) and quartile (Q)].

Basic information		Cases	Controls	P value
Age(year)	Male	62.07±7.49	61.83±7.44	0.780
	Female	61.86±8.40	61.80±8.29	0.952
	Total	61.98±7.90	61.82±7.84	0.812
Education level	Illiterate	127	227	0.090
	Primary school	54	103	
	Junior high school	21	60	
	Senior high school and above	5	24	
Marital status	Married	160	342	0.463
	Divorce	1	2	
	Widowed	42	64	
	Spinsterhood	4	6	

Table 1. Comparison of the basic information between cases and controls.

Food kinds	Cases	Controls	P value
Cereals	528.01±276.51	501.73±226.65	0.365
Livestock and poultry meat	38.90±43.08	24.02±32.87	0.008
Fish and shrimp	13.22±22.88	11.38±17.04	0.652
Egg, milk and products	27.95±44.38	27.40±39.56	0.384
Beans and products	79.79±70.30	69.45±77.82	0.341
Vegetables	214.26±227.26	247.70±167.12	0.967
Fruits	39.52±64.17	30.15±42.99	0.201
Allium vegetables	4.11±6.52	8.49±12.16	0.004
Salted and smoked products	34.38±44.86	37.78±46.05	0.718

Table 2. Foods dietary intakes of cases and controls (g/d, M±Q).

As shown in table 2, the large proportion of daily diet was plant-based foods such as cereals, vegetables and so on in both cases and controls. Because the data was not normally distributed, the wilcoxon signed rank test (non-parametric test method for two related samples) was used to compare the differences of various foods intakes between cases and controls. The daily intake of Allium vegetables of controls was significantly higher than that of cases ( $P<0.05$ ), while the daily intake of livestock and poultry meat of controls was significantly lower than that of cases ( $P<0.05$ ). Logistic regression analysis found that not eating garlic (OR=2.006, 95% CI: 1.451-2.774) and liking eating fat meat (OR=1.796, 95% CI: 1.249-2.584) were the risk factors for esophageal cancer.



The nutrients daily intakes for cases and controls were listed in table 3.

Nutrients	Cases	Controls	P value
Energy(KJ)	5460.27±3533.35	6191.34±3150.04	0.006
Protein(g)	50.02±35.08	57.33±30.89	0.045
Fat(g)	29.03±27.89	33.35±26.62	0.222
Carbohydrates(g)	213.70±140.49	253.84±109.67	0.002
Dietary Fibre(g)	11.87±11.21	13.63±10.12	0.088
Vitamin A(µgRE)	579.92±622.39	555.91±388.17	0.266
Thiamine(mg)	0.66±0.58	0.78±0.59	0.006
Riboflavin(mg)	0.74±0.62	0.78±0.44	0.267
Niacin(mg)	16.27±8.07	18.52±8.27	0.000
Vitamin C(mg)	67.09±77.45	75.52±51.83	0.393
Vitamin E(mg)	11.53±12.64	14.30±12.63	0.063
Calcium(mg)	388.35±351.61	444.40±318.82	0.049
Phosphorus(mg)	889.70±595.75	1041.79±522.61	0.016
Potassium(mg)	1499.53±1252.12	1602.00±933.45	0.235
Sodium(mg)	1312.31±1575.14	1442.03±1404.18	0.657
Magnesium(mg)	273.79±207.08	320.38±183.14	0.007
Iron(mg)	21.27±13.85	21.96±9.87	0.623
Zinc(mg)	11.26±6.20	11.71±5.72	0.093
Selenium(mg)	25.37±21.18	27.69±16.81	0.576
Copper(µg)	1.62±1.33	1.78±1.00	0.734

Table 3. The nutrients daily intakes of cases and controls(M±Q).

As shown in table 3, there were no significant difference between the daily intake of fat, dietary fiber, vitamin A, riboflavin, vitamin C, vitamin E, potassium, sodium, iron, zinc, selenium, and copper between cases and controls using wilcoxon signed rank test ( $P>0.05$ ). Meanwhile, the daily intakes of energy, protein, carbohydrate, thiamine, niacin, calcium, phosphorus, magnesium of controls were significantly higher than that of the cases ( $P<0.05$ ).

Nutrients	Intake level	P	OR	95%CI
Energy (KJ)	< 4353.18			
	4353.18-5902.73	0.006	0.456	0.260-0.801
	5902.73-7732.61	0.000	0.321	0.182-0.566
	> 7732.61	0.002	0.414	0.235-0.727
Protein (g)	< 39.06			
	39.06-54.73	0.106	0.633	0.364-1.101
	54.73-73.35	0.005	0.447	0.256-0.780
	> 73.35	0.012	0.492	0.282-0.858

Nutrients	Intake level	P	OR	95%CI
Carbohydrates (g)	< 173.88			
	173.88-230.01	0.009	0.471	0.268-0.829
	230.01-298.76	0.000	0.260	0.146-0.463
	> 298.76	0.002	0.411	0.233-0.725
Thiamine (mg)	< 0.45			
	0.45-0.73	0.859	1.051	0.609-1.814
	0.73-1.07	0.037	0.556	0.320-0.966
	> 1.07	0.043	0.565	0.325-0.983
Niacin (mg)	< 13.13			
	13.13-17.44	0.001	0.369	0.209-0.653
	17.44-21.68	0.001	0.369	0.209-0.653
	> 21.68	0.000	0.262	0.147-0.468
Calcium (mg)	< 288.65			
	288.65-419.98	0.042	0.563	0.323-0.980
	419.98-625.11	0.003	0.429	0.245-0.749
	> 625.11	0.012	0.491	0.281-0.857
Phosphorus (mg)	< 716.61			
	716.61-961.22	0.014	0.498	0.285-0.870
	961.22-1274.97	0.000	0.364	0.207-0.639
	> 1274.97	0.008	0.469	0.268-0.821
Magnesium (mg)	< 210.65			
	210.65-305.14	0.140	0.660	0.380-1.146
	305.14-409.08	0.015	0.504	0.289-0.876
	> 409.08	0.012	0.493	0.283-0.859

Table 4. ORs of nutrients different intake levels for the EC risk.

ORs of significant nutrients for EC were showed in Table 4. The highest intake quartiles of energy, protein, carbohydrate, thiamine, niacin, calcium, phosphorus and magnesium were associated with decrease in risk for EC compared with the lowest quartiles, the ORs were 0.414 (95%CI: 0.235-0.727), 0.492 (95%CI: 0.282-0.858), 0.411 (95%CI: 0.233-0.725), 0.565 (95%CI: 0.325-0.983), 0.262 (95%CI: 0.147-0.468), 0.491 (95%CI: 0.281-0.857), 0.469 (95%CI: 0.268-0.821), and 0.493 (95%CI: 0.283-0.859) respectively.

### 3.3 Discussion

#### 3.3.1 Allium vegetables

In China, the Allium vegetables include garlic, onions, leeks, green Chinese onions, garlic sprouts, and garlic bolt and so on. These vegetables are rich in vitamins, minerals and phytochemicals. Many studies have indicated that Allium vegetables have anticarcinogenic effect which is attributed to organosulfur compounds [e.g., diallyl sulfide, diallyl disulfide

(DADS), diallyl trisulfide (DATS), S-allyl cysteine (SAC), S-allylmercaptocysteine (SAMC), ajoene, etc.] (Stan et al., 2008). Our results indicated that the daily intake of Allium vegetables of controls was significantly higher than that of cases ( $P < 0.05$ ) and not eating garlic was a risk factor for EC, OR=2.006 (95%CI: 1.451-2.774). Our result was similar to before reports (Chen et al., 2009; Galeone et al., 2006; Takezaki et al., 2001).

### 3.3.2 Meat

This study found that the daily intake of livestock and poultry meat of cases was significantly higher than that of controls. The logistic regression analysis indicated that who like eating fat meat was a risk factor for EC, OR =1.796 (95%CI: 1.249-2.584). Eating meat and animal fat may promote the mechanism of EC with total fat and saturated fatty acid intake increased. Our result was consistent to other reports (Navarro Silvera et al., 2011; Silvera et al., 2008).

### 3.3.3 Dietary nutrients intakes

In recent years, researchers pay more attention to the relationship between nutrients and EC. Nutrients deficiency may play an assistant role in the process of carcinogenesis. We have found that the nutritional status of residents in Chuzhou area was poor compared with the low EC incidence area (Wang et al., 2005). In this case-control study we found that the energy, protein, carbohydrates intakes of cases were lower than that of controls ( $P < 0.05$ ). The highest intake quartiles of energy, protein, carbohydrate were associated with decreased risk for EC compared with the lowest quartiles, the ORs were 0.414 (95%CI 0.235-0.727), 0.492 (95%CI 0.282-0.858), and 0.411 (95%CI 0.233-0.725) respectively. Some reports have suggested that high carbohydrate and energy intakes and obesity can account for at least some of the rise in EAC (Thompson et al., 2008). In our study the cases were all ESCC and the energy intake of the participants was low. The percentage of participants whose energy intake reached the Chinese RNI was only 10% which was vulnerable to suffer from energy malnutrition. This may result in that the high energy intake is the protective factor for EC in this area. Protein is the material basis of all life. Inadequate intake of protein leads to physical decline, decreased immunity, prone to various diseases. Chen reported that greater intakes of dietary protein and carbohydrate were inversely associated with risk of EAC (Chen et al., 2002).

Many reports have supported that low vitamin intake may partly explain the high incidence of EC among inhabitants in high incidence areas (Bravi et al., 2011; De Stefani et al., 2006; Ibiebele et al., 2011; Malekshah et al., 2010). This study indicated that the highest intake quartiles of thiamine and niacin were both associated with decreased risk for EC compared with the lowest quartiles, the ORs were 0.565 (95%CI: 0.325-0.983) and 0.262 (95%CI: 0.147-0.468) respectively. The results suggested that inadequate intake of thiamine and niacin may be a risk factor for EC and were consistent with previous reports (Franceschi et al., 2000; Siassi et al., 2000).

Among minerals, the anti-cancer role of selenium and zinc were the research focus and some researchers reported that selenium and zinc were preventive factors for occurrence of EC (Cai et al., 2006; Lu et al., 2006; Wei et al., 2004). However our results did not find the relationship between selenium, zinc and EC. We found calcium, phosphorus, and

magnesium had protective action for occurrence of EC. There were reports that high phosphorus intake may decrease the risk of EC (Franceschi et al., 2000; Launoy et al., 1998; Siassi et al., 2000).

#### 4. Conclusions

The role of food and nutrients for EC causation has been a subject of considerable research. The results of our meta-analysis studies suggested that: 1) increased dietary vegetables and fruits decrease the risk of EC; 2) high intake of dietary vitamin A,  $\beta$ -carotene, folic acid and vitamin E were associated with decreased risk of EC; 3) drinking green tea was a protective factor against EC and maté drinking may be a risk factor for EC.

The case-control study suggested that: 1) increased dietary Allium vegetables intake such as garlic was associated with decreased risk of EC, while increased fat meat, livestock and poultry meat intake was associated with increased risk of EC; 2) high dietary intakes of energy, protein, carbohydrate, thiamine, niacin, calcium, phosphorus and magnesium may decrease the risk of EC in this area.

We need more studies especially cohort studies to explore the effects of foods and nutrients on the occurrence of EC. Moreover, the mechanism of the actions needs to be studied further too.

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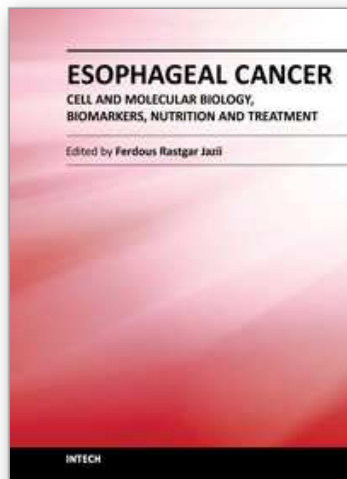
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Esophageal Cancer illustrates recent achievements and investigations in the esophageal tumorigenesis from different perspectives. Readers find mechanisms involved in esophageal tumorigenesis, cellular, molecular, genetic, epigenetics, and proteomics, their relevance as the novel biomarkers and application in esophageal cancer diagnosis and therapy. The book covers detailed effect of nutritional factors in addition to ethanol metabolic pathway in the inhibition of retinoic acid metabolism and supply. Diagnosis, classification, and treatment of esophageal cancer, application of both surgical and non surgical methods as well as follow up of the disease are described in detail. Moreover readers are endowed with especial features of esophageal cancer such as multiple early stage malignant melanoma and pulmonary edema induced by esophagectomy, the two features that received less attention elsewhere in literature.

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