

# Family history of esophageal cancer modifies the association of serum lipids and malignant esophageal lesions: a nested case-control study from the “Endoscopic Screening for Esophageal Cancer in China” trial

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## Abstract

**Background:** The association of lipids and cancer has varied greatly among different cancer types, lipid components and study populations. This study is aimed to investigate the association of serum lipids and the risk of malignant lesions in esophageal squamous epithelium.

**Methods:** In the “Endoscopic Screening for Esophageal Cancer in China” (ESECC) trial, serum samples were collected and tested for total cholesterol (TC), triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol at the time of subject enrollment. Cases were defined as malignant esophageal lesions identified by baseline endoscopic examination or by follow-up to May 31, 2018. Controls were randomly selected using incidence density sampling in the same cohort. Conditional logistic models were applied to identify the association of serum lipids and the risk of malignant esophageal lesions. Effect modification was evaluated by testing interaction terms of the factor under assessment and these serum lipid indicators.

**Results:** No consistent association between serum lipid levels and esophageal malignant lesions were found in a pooled analysis of 211 cases and 2101 controls. For individuals with a family history of esophageal cancer (EC), high TC, and LDL-C were associated with a significantly increased risk of having malignant lesions (odds ratio [OR]<sub>High vs. Low TC</sub> = 2.22, 95% confidence interval [CI]: 1.14–4.35; OR<sub>High vs. Low LDL-C</sub> = 1.93, 95% CI: 1.01–3.65). However, a negative association was observed in participants without an EC family history (OR<sub>High vs. Low TC</sub> = 0.69, 95% CI: 0.48–0.98,  $P_{\text{interaction}} = 0.002$ ; OR<sub>High vs. Low LDL-C</sub> = 0.50, 95% CI: 0.34–0.76,  $P_{\text{interaction}} < 0.001$ ).

**Conclusions:** In this study, we found that the association of serum lipids and malignant esophageal lesions might be modified by EC family history. The stratified analysis would be crucial for population-based studies investigating the association of serum lipids and cancer. The mechanism by which a family history of EC modifies this association warrants further investigation.

**Keywords:** Effect modification; Esophageal squamous cell carcinoma; Family history; Genetic susceptibility; Lipids and lipoprotein

## Introduction

Abnormalities in lipid and lipoprotein metabolism are associated with various diseases. It is well established that elevated levels of the low-density lipoprotein increase risk of cardiovascular diseases (CVD).<sup>[1,2]</sup> Associations correlation of lipids and occurrence of cancer have been studied since the 1990s,<sup>[3-7]</sup> and evidence from epidemiologic studies as well as laboratory research has demonstrated a

close relationship between lipid metabolism and carcinogenesis.<sup>[8-15]</sup>

However, the magnitude of this influence and whether it is positive or negative in the association of blood lipid on cancer

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has varied greatly among different cancer types, lipid components, and study populations in previous studies.<sup>[11]</sup> Moreover, in individuals with or without environmental or behavioral exposures (eg, cigarette smoking, alcohol consumption, and obesity), the associations of lipids and cancer identified are commonly different or even opposite.<sup>[13]</sup> It raises the possibility that variation in pooled association estimates may be caused by a mixture of varying associations among subgroups within populations. As a result, effect modifications among subgroup(s) of subjects with specific characteristics must be critically addressed.

Esophageal cancer (EC) is one of the most frequent causes of cancer-related mortality worldwide and results in 508,000 deaths annually.<sup>[16]</sup> In contrast to esophageal adenocarcinoma in western countries, 90% of EC cases in China are esophageal squamous cell carcinoma (ESCC).<sup>[17,18]</sup> Up to this time, only one population-based study with 14 years of follow-up data from 1,189,719 Korean adults has reported an association of serum lipids and risk of having ESCC. This study suggests that high levels of total cholesterol (TC) slightly lower the risk of having EC in men, but no association of TC with cancer was observed in women.<sup>[14]</sup> However, this study focused mainly on evaluating the association of blood lipids and Korean highly prevalent cancers such as stomach, lung, and liver cancer, and did not pay much attention to the analysis of subgroups and evaluation of the magnitude and positive or negative direction of influence of the association among subgroups in this population.

Previously, we have reported the prevalence characteristics of dyslipidemia from a large-scale population-based randomized controlled trial in rural China.<sup>[19]</sup> In this study, we investigated the association of serum lipids and malignant esophageal lesions of the squamous epithelium based on incidence density matched cases and controls. A series of exposure variables (eg, age, gender, family history of EC, cigarette smoking, alcohol drinking, body mass index [BMI], etc) that would potentially modify the association of blood lipids and the occurrence of malignant esophageal lesions in subgroups were also carefully evaluated.

## Methods

### Ethical approval

Research protocols for the present study were approved by the Institutional Review Board of the Peking University School of Oncology, Beijing, China (No. 2011101110). Informed consent was obtained from all participants.

### Parent study

In 2012, we initiated the Endoscopic Screening for Esophageal Cancer in China (ESECC) randomized controlled trial (Trial Registration: ClinicalTrials.gov, NCT01688908; <https://clinicaltrials.gov/ct2/results?recrs=&cond=&term=01688908&cntry=&state=&city=&dist>) in Hua County, Henan Province, China. This trial was designed to evaluate the efficacy and cost-effectiveness of endoscopic screening for EC, and the original design of this trial may be found elsewhere.<sup>[20]</sup> Briefly, 668 villages were randomly selected

from Hua County, and these villages were allocated to the screening arm or control arm of the study at a ratio of 1:1 through a blocked randomization procedure. Residents between 45 and 69 years of age in targeted villages were enrolled as participants. Blood samples were collected from all participants at enrollment. In the baseline investigation, all participants had a physical examination which included measurement of height, weight, and blood pressure. A computer-aided one-on-one questionnaire survey was conducted for all participants by trained interviewers, and information regarding demographic factors, lifestyle information, ESCC-related symptoms, and ESCC family history was collected. Participants in the screening arm underwent standard endoscopic examination and biopsy with iodine staining at baseline investigation. No screening was undertaken in the control arm. Recruitment and screening for this ESECC trial were completed in September 2016. The annual follow-up to evaluate for incident cancer cases and deaths from all causes in this population are ongoing, and information regarding cancer diagnosis, date of diagnosis, cause of death, date of death, and International Classification of Diseases (10th revision) code was collected through active door-to-door interviews or passive linkage with local electronic registry data.<sup>[21]</sup>

### Study design and participants

This study was a nested case-control study based on the ESECC trial. Eligibility criteria included: (1) ESECC cohort members; (2) questionnaire completed; (3) blood samples provided with valid test results for serum lipids. Cases were designated as malignant esophageal lesions (severe dysplasia, carcinoma *in situ*, or ESCC) identified at an endoscopic examination or at the annual follow-up to May 31, 2018. For each case, ten controls were randomly selected using incidence density sampling with matched gender, age at enrollment (5-year age group), family history of EC, and status of subject acceptance of screening from the ESECC population.

### Measurement of serum lipids

A fasting blood sample of ~5 mL was collected from each participant in a heparin sodium anticoagulant tube at enrollment. These tubes were centrifuged at 1000 r/min for 5 min and the supernatant was sent within 4 h for lipid measurement of TC, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) to the clinical laboratory of the Hua County People's Hospital. Lipid measurements were conducted using a HITACHI7600 automatic biochemistry analyzer (Hitachi High Technologies Co., Tokyo, Japan) with commercially available reagents (Autobio Diagnostics Co., Ltd., Beijing, China) for analysis of TC, TG, LDL-C, and HDL-C.

### Statistical analysis

The Chi-square test and Wilcoxon rank-sum test were used to compare baseline characteristics and risk factors of cases and matched controls. Univariable and Multivariable conditional logistic regression models were applied to evaluate the association of each blood lipid indicator and

the risk of malignant esophageal lesions. In the multivariable model, adjustments were made for risk factors for ESCC previously identified in this population including age, gender, family history of EC, BMI, coal stove for heating, fume exposure in the kitchen, fast eating speed, and ingestion of leftovers.<sup>[20]</sup> In this study, two approaches were applied for the classification of raw serum lipid levels generated by the biochemistry analyzer. For dichotomized classification, lipid levels were first separated into “high” and “low” values with a specific cutoff, and multivariable logistic regression was fitted to generate a risk estimate (odds ratio [OR]) of high *vs.* low serum lipid levels for this cutoff. A series of increasing stepwise cutoff points (every 10 mg/dL) from the 5% quantile to the 95% quantile in control subjects were then tested, and a curve of ORs together with a different set of cutoff points was generated to assess the effect size and consistency of the association which was detected. We also classified each lipid indicator into five categories by quintiles in control subjects and calculated the risk estimates for each quintile of subjects by setting the lowest quintile as the reference group.

Effect modification in this study was evaluated by adding an interaction term of the factor under assessment (age, gender, family history of EC, BMI, smoking, and alcohol consumption) and serum lipid indicators one at a time in the adjusted multivariable model. The coding form of variables assessed in effect modification analysis can be found in Supplementary Table 1, <http://links.lww.com/>

CM9/A502. Stratified analysis was applied and ORs were estimated separately in subgroups when significant interaction *P* values were detected. The optimal cutoff point, which maximized the heterogeneity of risk estimates between subgroups of individuals, was chosen as the cutoff point resulting in the minimum Akaike information criterion (AIC). Statistical analysis was performed using STATA (Version 13.1; Stata Corp LLC, College Station, USA). All tests were two-sided and *P* values < 0.05 were considered statistically significant.

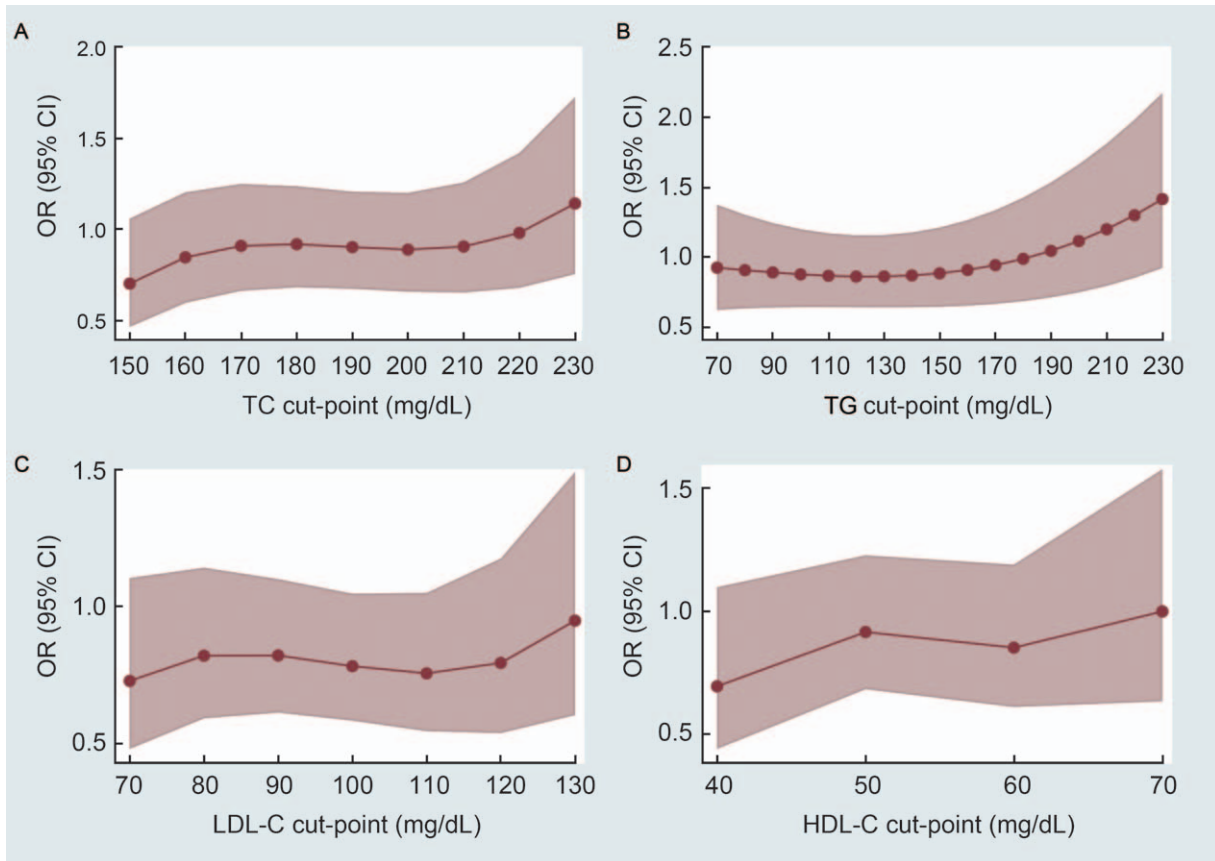
### Results

A total of 211 cases and 2101 matched controls were enrolled in this study [Supplementary Figure 1, <http://links.lww.com/CM9/A502>]. All cases were matched with ten controls except that a single case was matched with nine controls and four cases matched with eight controls due to the limited number of candidate control cases. Age, gender, and family history of EC were well balanced between the case and control groups. Cases had significantly lower BMI ( $Z = 2.370, P = 0.018$ ) compared with control subjects. There were no significant differences identified for other ESCC risk factors in the ESECC population [Table 1]. The median levels of TC, TG, LDL-C, and HDL-C for cases were 189, 117, 97, and 53 mg/dL, and median levels for controls were 185, 113, 96, and 52 mg/dL, respectively. No statistically significant differences were found for these four lipid indices comparing cases and controls.

**Table 1: Baseline characteristics and distribution of serum lipid levels among participants enrolled in the current study.**

Variables	Controls (n = 2101)	Cases (n = 211)	Z or $\chi^2$ value	P value*
Age (years)	63 (60–66)	63 (60–66)	-0.052	0.958
Gender			0.0002	0.990
Male	1156 (55.02)	116 (54.98)		
Female	945 (44.98)	95 (45.02)		
Family history of EC			0.014	0.905
No	1690 (80.44)	169 (80.09)		
Yes	411 (19.56)	42 (19.91)		
BMI (kg/m <sup>2</sup> )	24.80 (22.50–27.39)	24.09 (21.67–26.84)	2.370	0.018
Coal stove for heating			0.424	0.515
No	1256 (59.78)	131 (62.09)		
Yes	845 (40.22)	80 (37.91)		
Fume exposure in kitchen			0.432	0.511
No	534 (25.42)	58 (27.49)		
Yes	1567 (74.58)	153 (72.51)		
Fast eating speed			2.099	0.147
No	372 (17.71)	29 (13.74)		
Yes	1729 (82.29)	182 (86.26)		
Ingestion of leftovers			0.303	0.582
≤1/week	1236 (58.83)	120 (56.87)		
>1/week	865 (41.17)	91 (43.13)		
TC (mg/dL) <sup>†</sup>	189 (166–212)	185 (166–211)	0.724	0.469
TG (mg/dL) <sup>‡</sup>	117 (85–168)	113 (81–163)	1.006	0.314
LDL-C (mg/dL) <sup>†</sup>	97 (82–114)	96 (79–108)	1.805	0.071
HDL-C (mg/dL) <sup>†</sup>	53 (45–61)	52 (44–60)	0.948	0.343

Data are presented as mean (quartile) or *n* (%). \*The Chi-square test and rank-sum test were used to compare demographic characteristics and behavioral factors among cases and controls included in this study. <sup>†</sup>To convert cholesterol to mmol/L, multiply values by 0.0259. <sup>‡</sup>To convert TG to mmol/L, multiply values by 0.0113. BMI: Body mass index; EC: Esophageal cancer; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglycerides.



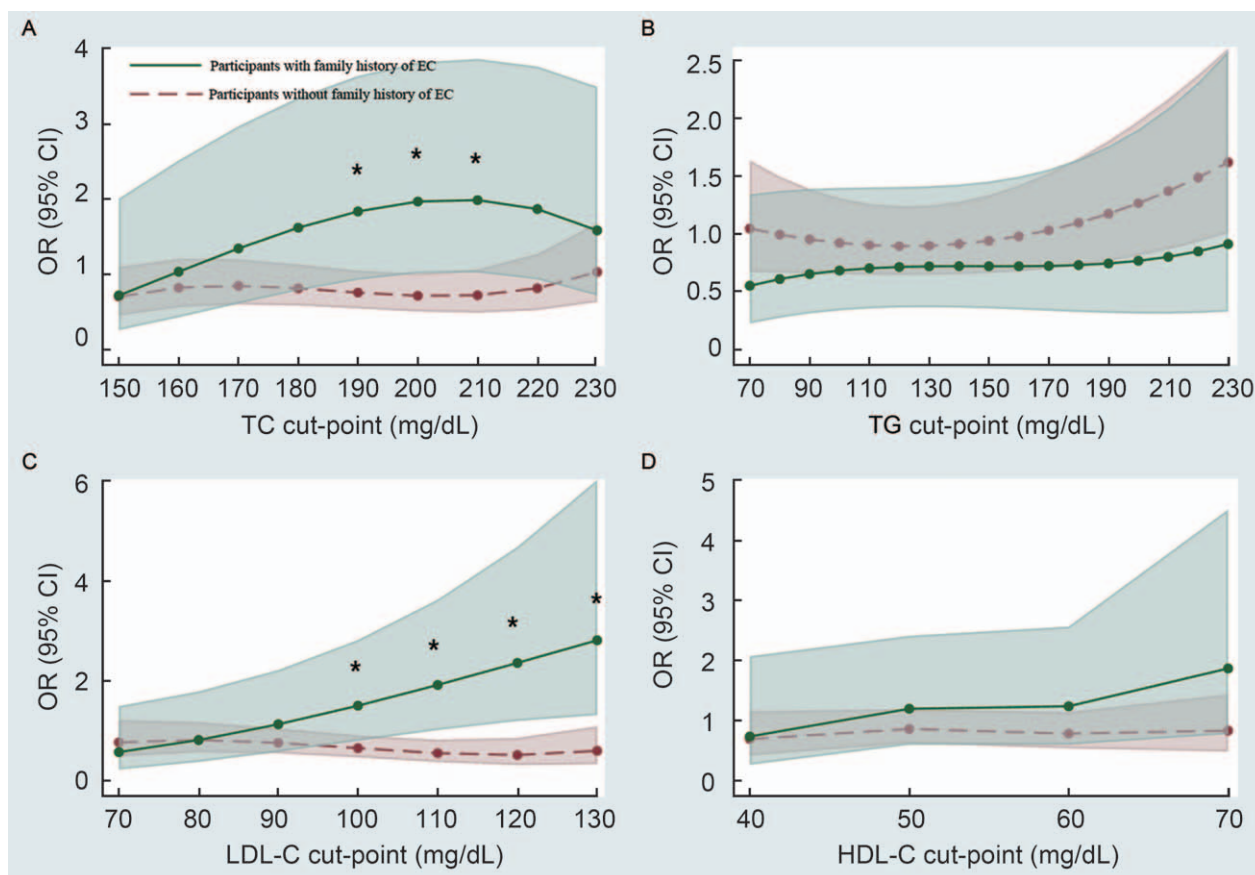
**Figure 1:** ORs and 95% CIs of each serum lipid indicator generated from the dichotomized classification with cutoff shifting algorithms ranging from 5% to 95% quartile\*. (A) The ORs and 95% CIs of TC and malignant esophageal lesions. (B) The ORs and 95% CIs of TG and malignant esophageal lesions. (C) The ORs and 95% CIs of LDL-C and malignant esophageal lesions. (D) The ORs and 95% CIs of HDL-C and esophageal malignant lesions. \*In multivariable models, adjustments were made for risk factors for ESCC previously identified in this population including age, gender, family history of EC, BMI, coal stove for heating, fume exposure in kitchen, fast eating speed, and ingestion of leftovers. BMI: Body mass index; CI: Confidence interval; EC: Esophageal cancer; ESCC: Esophageal squamous cell carcinoma; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; ORs: Odds ratios; TC: Total cholesterol; TG: Triglycerides.

Almost no significant associations were found between either the dichotomized or the quintile-classified TC, TG, and HDL-C levels and malignant esophageal lesions in the study population as shown in Figure 1 and Supplementary Figure 2, <http://links.lww.com/CM9/A502>. LDL-C was associated with a decreased risk of malignant esophageal lesions for certain cutoff points (100 mg/dL), but this association was not consistent when cutoff values were shifted [Figure 1].

Evaluation of associations among subgroups defined by potential effect modification variables showed that a family history of EC was found to modify the association of serum lipids (TC and LDL-C) and esophageal malignancy ( $Z = 2.41$ ,  $P_{interaction} = 0.016$  for TC;  $Z = 2.48$ ,  $P_{interaction} = 0.013$  for LDL-C) [Supplementary Table 2, <http://links.lww.com/CM9/A502>]. In a stratified analysis using the stepwise cutoff-increasing algorithm, high levels of TC and LDL-C were consistently associated with an increased risk of malignant esophageal lesions in subjects with a family history of ESCC. Conversely, in subjects without a family history of high levels of TC and LDL-C decreased the risk of malignant esophageal lesions. Statistically significant effect modification was found at cutoff values ranging from 190 to 210 mg/dL for TC and

100 to 130 mg/dL for LDL-C [Figure 2]. Results were similar for quintile-based cutoffs, suggesting lipids play varying roles in subjects with or without a family history of EC [Supplementary Figure 3, <http://links.lww.com/CM9/A502>].

Using AIC as the selection criteria, the optimal cutoff points for maximizing heterogeneity between subgroups were set as 200, 230, 110, and 40 mg/dL for TC, TG, LDL-C, and HDL-C, respectively [Figure 2]. Table 2 demonstrates the association of serum lipid indicators and malignant esophageal lesions based on the selected cutoff values using AIC, stratified according to whether the study subject had a family history of EC or not. For individuals with a family history, high-level group of TC ( $\geq 200$  mg/dL) and LDL-C ( $\geq 110$  mg/dL) were accompanied by a significantly increased risk of malignant lesions (TC:  $OR_{High\ vs.\ Low} = 2.22$ , 95% CI: 1.14–4.35; LDL-C:  $OR_{High\ vs.\ Low} = 1.93$ , 95% CI: 1.01–3.65). However, a significantly negative association was observed for participants without a family history (TC:  $OR_{High\ vs.\ Low} = 0.69$ , 95% CI: 0.48–0.98; LDL-C:  $OR_{High\ vs.\ Low} = 0.50$ , 95% CI: 0.34–0.76), and distinct heterogeneity was found between individuals in these two subgroups (TC:  $Z = 3.11$ ,  $P_{interaction} = 0.002$ ; LDL-C:  $Z = 3.62$ ,  $P_{interaction} < 0.001$ ).



**Figure 2:** ORs and 95% CIs of each serum lipid indicator generated from the dichotomized classification with cutoff shifting algorithms ranging from 5% to 95% quantile, stratified by the status of family history of EC<sup>†</sup>. (A) The ORs and 95% CIs of TC and malignant esophageal lesion, stratified by status of family history of EC. (B) The ORs and 95% CIs of TG and malignant esophageal lesion, stratified by status of family history of EC. (C) The ORs and 95% CIs of LDL-C and malignant esophageal lesion, stratified by status of family history of EC. (D) The ORs and 95% CIs of HDL-C and malignant esophageal lesions, stratified by status of family history of EC. \*Significant interaction *P* values (<0.05) were achieved under these cutoff points. <sup>†</sup>In multivariable models, adjustments were made for risk factors for ESCC previously identified in this population including age, gender, family history of EC, BMI, coal stove for heating, fume exposure in kitchen, fast eating speed, and ingestion of leftovers. BMI: Body mass index; CI: Confidence interval; EC: Esophageal cancer; ESCC: Esophageal squamous cell carcinoma; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; ORs: Odds ratios; TC: Total cholesterol; TG: Triglycerides.

In addition, we performed a sensitivity analysis by excluding prevalent ESCC cases detected within 12 months of blood lipid measurement, and the effect modification of family history status remained significant [Supplementary Table 3, <http://links.lww.com/CM9/A502>]. To assess the impact of cholesterol-lowering drug use on the association of serum lipid indicators and malignant esophageal lesions, we also performed a sensitivity analysis by excluding participants with self-reported CVD or history of diabetes in this study. A similar association and significant effect modification involving TC and LDL-C were still found [Supplementary Table 4, <http://links.lww.com/CM9/A502>].

**Discussion**

The association of serum lipids and cancer has been studied since the 1990s. To date, the associations identified in population-based prospective studies have varied markedly, primarily due to differences in populations, tissue specificity, and the complexity of lipid metabolism itself. Genetic and environmental factors and the potential interactions between them may also contribute to the inconsistencies in these associations, which may bias

conclusions. This study is a prospective nested case-control study designed to investigate the association of serum lipids and the risk of malignant esophageal lesions in the squamous epithelium based on a large-scale population-based randomized controlled trial in rural China. We found almost no association between serum lipid levels and malignant esophageal lesions in the study population, which is consistent with a previous study.<sup>[14]</sup> However, stratified analysis revealed notable heterogeneity in the association of serum lipids and malignant esophageal lesions based on the status of family history of EC in the study subjects. That is, elevated levels of TC and LDL-C were associated with an increased risk of esophageal malignancy for subjects with a family history of EC but showed decreased risk for subjects without a family history of EC. Results from this study may provide an impetus for further study of the etiology and risk stratification of ESCC.

Serum lipid abnormalities are correlated with the development of many different diseases. In many cases, the determination of the specific role serum lipid(s) play in these diseases is not straightforward, as serum lipid is regulated by a complex network of other molecules. As

**Table 2: Independent associations of serum lipids with EC risk in a stratification of family history of EC under the AIC-selected cutoff.**

Variables	Participants without a family history of EC (n = 1859)			Participants with a family history of EC (n = 453)			Z value for interaction	P value for interaction
	Cases (n)/controls (n)	Crude OR (95% CI)	Adjusted OR (95% CI)*	Cases (n)/controls (n)	Crude OR (95% CI)	Adjusted OR (95% CI)*		
TC							3.11	0.002
Low (<200 mg/dL)	120/1058	Ref	Ref	17/243	Ref	Ref		
High (≥200 mg/dL)	49/632	0.67 (0.47–0.96)	0.69 (0.48–0.98)	25/168	2.20 (1.14–4.26)	2.22 (1.14–4.35)		
TG							–1.11	0.266
Low (<230 mg/dL)	146/1525	Ref	Ref	38/364	Ref	Ref		
High (≥230 mg/dL)	23/165	1.47 (0.91–2.36)	1.62 (1.00–2.62)	4/47	0.81 (0.28–2.38)	0.83 (0.28–2.45)		
LDL-C							3.62	<0.001
Low (<110 mg/dL)	138/1164	Ref	Ref	22/282	Ref	Ref		
High (≥110 mg/dL)	31/526	0.50 (0.33–0.74)	0.50 (0.34–0.76)	20/129	1.94 (1.03–3.65)	1.93 (1.01–3.65)		
HDL-C							0.04	0.968
Low (<40 mg/dL)	19/144	Ref	Ref	5/38	Ref	Ref		
High (≥40 mg/dL)	150/1546	0.74 (0.44–1.22)	0.69 (0.41–1.15)	37/373	0.72 (0.26–2.03)	0.73 (0.26–2.07)		

\*In multivariable models, adjustments were made for risk factors for ESCC previously identified in this population including age, gender, family history of EC, BMI, coal stove for heating, fume exposure in kitchen, fast eating speed, and ingestion of leftovers. AIC: Akaike information criterion; BMI: Body mass index; EC: Esophageal cancer; ESCC: Esophageal squamous cell carcinoma; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; OR: Odds ratio; TC: Total cholesterol; TG: Triglycerides.

such, a traditional pooled analysis that ignores interactions (heterogeneity) may be inappropriate, while stratified epidemiology has the power for the identification of real associations, which may serve to reduce controversial results in the study of serum lipids and cancer. Based on this concept, we suggest that genetic or environmental variables that have the potential for effect modification be subjected to more intensive evaluation in epidemiologic studies investigating the association of serum lipids and cancer.

Considering the design of ESCC screening projects, the interaction of associations detected in stratified analysis in this study may also be useful for the identification of individuals at high risk for ESCC. We previously established a prediction model for ESCC based on questionnaire investigation, and this model can significantly decrease endoscopic screenings by distinguishing a subgroup at high risk for ESCC in the general population.<sup>[22]</sup> According to the findings of the current study, evaluation of serum lipid levels coupled with a family history of EC may be expected to enhance the ability of this model to differentiate high-risk individuals. In addition, the AIC-chosen cutoffs for the serum lipid indicators were extremely close to the recommended threshold for borderline high dyslipidemia according to the guidelines for the prevention and treatment of dyslipidemia in Chinese adults.<sup>[23]</sup> We therefore also performed a stratified analysis based on the cutoff values recommended by the “CVD relevant guideline.” This stratified analysis yielded a similar association and significant effect modification involving TC and LDL-C [Supplementary Table 5, <http://links.lww.com/CM9/A502>]. It is still unclear whether there is a connection between EC and risk of CVD in

subgroups of individuals with or without a family history of EC, and further epidemiologic studies together with mechanistic studies are needed to evaluate this observed concordance of disease risk.

Two main strengths of this study when compared with previous hospital-based case-control studies should be noted. As this is a nested case-control study based on an ongoing large population-based randomized trial, the study sample is ideally representative and guarantees cases and controls can be compared. Moreover, serum samples were collected and tested before the onset of clinical-stage ESCCs in this study, which reduced the possibility of false positives due to the energy expenditure and metabolic disorder that may be found in advanced stages of cancer.

The biological mechanisms underlying the heterogeneous associations of serum lipids and the risk of malignant esophageal lesions in subjects with and without a family history of EC are thus far unclear. Here, we can propose a possible mechanistic explanation based on the observed heterogeneous effects and the biological significance of the family history of EC, which may imply this study for future genetic research. A family history of cancer is widely accepted as a collective representation of genetic susceptibility.<sup>[24]</sup> One explanation for the heterogeneous associations which are observed is that serum lipid levels are an agent of gene function alteration involved in the process of carcinogenesis, and alteration of driver genes may vary significantly according to varying levels of genetic susceptibility. This explanation was supported by two studies evaluating the association of single-nucleotide polymorphisms (SNPs), the main contributor to genetic susceptibility to cancer, and ESCC according to the status

of family history. In Suo *et al*'s<sup>[25]</sup> investigation, eight and 16 SNPs with no shared loci were found to be associated with familial and non-familial ESCC, and through functional prediction, some were located in pathways of lipid metabolism. Another genome-wide association study compared genetic alterations in familial and non-familial ESCC, and the rs79747906 locus was found to be associated with a family history of EC.<sup>[26]</sup> This variant is associated with metabolic traits by alteration of the expression of LPIN2,<sup>[26]</sup> which is an important enzyme in triglyceride metabolism. These studies altogether suggested that genetic alternations were different between familiar and non-familiar ESCC, and a certain proportion of these genetic alternations might be located in lipids metabolism pathways and cause discrepancies in lipid profiles. However, the study design and experimental methodology in the above two studies limit their ability to uncover lipid-related genes or loci corresponding to the development of familial or sporadic ECs, and further stratified analysis based on the status of ESCC family history is needed in large-scale genomic studies.

Our study has limitations. First, we are unable to conclude the causality of malignant esophageal lesions resulting from dyslipidemia, even though lipid measurement was performed before case identification. In addition, although the current study was based on a large-scale population-based trial with 34,000 participants, only 211 cases of malignant esophageal lesions from a single study area were included in the study, which limits the generalizability of conclusions from this study. Further evaluation in other study populations is needed to validate these results.

We conclude that high levels of TC or LDL-C were associated with an increased risk of malignant esophageal lesions in subjects with a family history of EC but were associated with decreased risk for subjects with no family history of EC. Moreover, these opposing effects yielded no association when subgroups of subjects were pooled together. This finding underlines the necessity of the application of stratified epidemiology in population-based studies evaluating the association of serum lipid and cancer. The mechanism involved in the modification of the association of serum lipids and malignant esophageal lesions with a family history of EC warrants investigation in additional family based genomic studies.

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### Conflicts of interest

None.

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