Associations between cancer family history and esophageal cancer and precancerous lesions in high-risk areas of China

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Abstract

Background: Family clustering of esophageal cancer (EC) has been found in high-risk areas of China. However, the relationships between cancer family history and esophageal cancer and precancerous lesions (ECPL) have not been comprehensively reported in recent years. This study aimed to provide evidence for identification of high-risk populations.

Methods: This study was conducted in five high-risk areas in China from 2017 to 2019, based on the National Cohort of Esophageal Cancer. The permanent residents aged 40 to 69 years were examined by endoscopy, and pathological examination was performed for suspicious lesions. Information on demographic characteristics, environmental factors, and cancer family history was collected. Unconditional logistic regression was applied to evaluate odds ratios between family history related factors and ECPL.

Results: Among 33,008 participants, 6143 (18.61%) reported positive family history of EC. The proportion of positive family history varied significantly among high-risk areas. After adjusting for risk factors, participants with a family history of positive cancer, gastric and esophageal cancer or EC had 1.49-fold (95% confidence interval [CI]: 1.36–1.62), 1.52-fold (95% CI: 1.38–1.67), or 1.66-fold (95% CI: 1.50–1.84) higher risks of ECPL, respectively. Participants with single or multiple first-degree relatives (FDR) of positive EC history had 1.65-fold (95% CI: 1.47–1.84) or 1.93-fold (95% CI: 1.46–2.54) higher risks of ECPL. Participants with FDRs who developed EC before 35, 45, and 50 years of age had 4.05-fold (95% CI: 1.30–12.65), 2.11-fold (95% CI: 1.37–3.25), and 1.91-fold (95% CI: 1.44–2.54) higher risks of ECPL, respectively.

Conclusions: Participants with positive family history of EC had significantly higher risk of ECPL. This risk increased with the number of EC positive FDRs and EC family history of early onset. Distinctive genetic risk factors of the population in high-risk areas of China require further investigation.

Trial registration: ChiCTR-EOC-17010553.

Keywords: Esophageal cancer; Family history; High-risk area; Cross-sectional study

Introduction

Esophageal cancer (EC) is the sixth leading cause of cancer death in the world.[1] Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma are two main pathological types of EC. Historically, ESCC is predominant in China, for it accounts for half of the world's total cases.[2] There are many risk factors for ESCC, including hot food,[3] smoking,[4] alcohol consumption,[5] nutrient deficiency,[6] poor oral health,[7] and polycyclic aromatic hydrocarbon exposure.,[8]

In addition to environmental risk factors, genetic ones also play important roles in the development of ESCC.[9] Previous studies found that the high-incidence areas of ESCC in China had obvious spatial clustering and family aggregation characteristics.[10–15] In provinces such as Shanxi[16] and Jiangsu,[17] case-control studies had been carried out to explore the association of genetic factors and ESCC. However, since significant differences existed between regions and populations in China, the results of single-center study were not sufficient to comprehensively report the relationship between family history and ESCC in the Chinese population. At the same time, the sample sizes of previous studies were also small, and the investigations of relevant indicators on genetic history were not enough. Based on genome-wide association

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study on ESCC in Han Chinese, some follow-up studies examined the single nucleotide polymorphisms (SNPs) associated with family history of ESCC. These studies found SNPs were related to family history and ESCC, such as rs79747906,[18] rs238415, rs1618536,[19] and rs2274223.[20] However, the sequencing results did not explain the genetic effects sufficiently, and its application in certain fields including high-risk population modeling was limited. Moreover, the main outcome of these studies was ESCC, and there was inadequate research information on precancerous lesions of the esophagus. Family history may be an indicator that can better reflect individual genetic risk factors and qualifies as pertinent to be included in the prediction models of high-risk population identification[21] However, there remains a lack of in-depth information and research on the relationship between family history and esophageal cancer and precancerous lesions (ECPL).

Therefore, we designed a multi-centered observational study using baseline data of the National Cohort of Esophageal Cancer (NCEC) to estimate the associations between cancer family history and ECPL in high-risk areas of China. This study can provide scientific evidence for the identification of high-risk populations and will be a gateway to further genetic epidemiologic research on ECPL.

Materials and methods

Ethics approval

The study was approved by the Ethics Committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Approval No. 16–171/250). The patients/participants provided their written informed consent to participate in this study.

Study areas and participants

This research is conducted based on NCEC. The study design previously was described in detail.[22] In brief, a population-based multi-centered cohort was set up in five counties of China, namely Cixian (Hebei), Linzhou (Henan), Feicheng (Shandong), Yangzhong (Jiangsu), and Yanting (Sichuan). Participants' enrollment began on 1st June 2017 and concluded by 31st December 2019. The five sites were major EC high-risk areas with incidence rates ranging from 35.52/100,000 to 81.23/100,000.[23]

Permanent residents of five study areas aged 40 to 69 years were eligible for inclusion, unless they had a history of cancer, mental disorder or contraindications for endoscopic examinations and were unable to provide informed consent.

This cohort experiment strictly abided by the relevant laws, and all research subjects had signed informed consent forms before being enrolled in the group. Confidentiality was strictly maintained as we concealed all personal information in the questionnaires while managing and analyzing the data under the supervision of the Ethics Committee.

Examination

Participants underwent iodine staining endoscopic examinations conducted by trained doctors in local cancer hospitals. The entire esophagus was visually examined, and biopsy samples were taken from all the focal lesions.[22] The pathology diagnostic results were mainly divided into two groups, i.e., (1) participants were designated as negative cases if diagnosed as normal or having esophagitis/basal cell hyperplasia (BCH) and (2) participants were designated as positive cases if diagnosed as low-grade intraepithelial neoplasia (LGIN), high-grade intraepithelial neoplasia (HGIN), and EC.

Data collection

We used cohort baseline data to conduct this study. The trained investigators performed a face-to-face survey using standard questionnaires, and participants answered the questions by themselves. Basic demographic information, risk factors, family history, and physical examination information were collected. The baseline questionnaire included age at enrollment, gender, education level, source of drinking water, cigarette smoking, consumption of alcohol, dietary habits, and family history of cancer. The collected information of family history included the number of relatives with positive cancer history, each relative's relationship, cancer diagnosis and onset age. Relative's relationships included 26 common types, which were further classified into two groups. First-degree relatives (FDR) included parents, siblings, and children, while second-degree relatives (SDR) included grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings. Other relationship types were not included in the analysis. All cancer cases were classified according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).

Quality control

All biopsy slides were examined by two pathologists independently. Discordances in diagnosis were solved by discussion. If there was no abnormality after iodine staining, tissue biopsy was not taken and was diagnosed as normal.

All investigators had been professionally trained for this cohort, and there were regular inspections by quality control personnel. Every questionnaire result was directly entered into the electronic system by using a pad-based direct data entry app, and the survey time and option frequency of each question were automatically detected in the system.

Statistical analysis

The EC onset age of relatives was used for classification, and ages 35, 40, 45, and 50 were selected as the cut-off values. When the relative's onset age of EC was less than the cut-off value, the participant was defined as an individual with positive EC family history of early-onset.

For continuous variables with normal distribution, the mean value was calculated and t test was performed. For

continuous variables with abnormal distribution, the Wilcoxon test was performed. For categorical variables, percentages were calculated, and the chi-squared test was performed. Unconditional logistic regression was used to explore the association between family history related factors and pathological diagnosis of the esophagus. Factors with statistically different distributions between the pathologically positive and negative groups were considered as confounding factors. Confounding factors and family history related factors were incorporated into the regression model. The odds ratio (OR) and 95% confidence intervals (95% CI) were reported. A significance level of 0.05 and two-sided tests were used throughout. All the data cleaning and analysis were undertaken via SAS software (version 9.4, SAS Institute Inc., Cary, USA).

Results

A total of 63,415 subjects were enrolled in the NCEC in five regions between 2017 and 2019. Then, 33,008 subjects with complete family history information and diagnosis results were included in this study. Among them, 2307 (6.99%) participants were diagnosed as LGIN/HGIN/EC and were defined as positive cases. Therefore, 30,701 (93.01%) were diagnosed as normal/esophagitis/BCH and were defined as negative cases. The mean age of the positive participants was 60.03 ± 6.17 years. The mean age of the negative participants was 54.99 ± 7.47 years. Compared with the negative participants, the positive participants were older and had a higher proportion of males. The positive cases also had higher smoking rate and higher alcohol consumption rate. Proportions of positive cases were higher in Feicheng and Linzhou. Compared with the negative participants, the positive participants had lower education levels and less access to filtered water. There were no significant differences with respect to hot food, vegetables, and fruit consumption [Table 1].

There were 13,547 (41.04%) participants who reported positive cancer family history. There were 8652 (26.21%) and 6143 (18.61%) people with gastric and esophageal cancer (GEC) and EC family history in high-risk areas, respectively. The number of participants with EC family history in FDR and SDR was 5011 (15.18%) and 1361 (4.12%), respectively. The proportions of EC family history were significantly different between the five high-risk areas. Yanting had the lowest proportion of EC family history (475, 11.86%), and Linzhou had the highest proportion (736, 26.56%) [Table 2].

Table 1: Associations between lifestyle risk factors and esophageal pathologic diagnoses.

Factors	Normal/esophagitis/BCH	LGIN/HGIN/EC	Statistics values	*P* value
Total	30,701	2307	–	–
Age (years)	54.99 ± 7.47	60.03 ± 6.17	−37.29*	<0.01
Gender			47.61†	<0.01
Male	12,520 (40.78)	1110 (48.11)		
Female	18,181 (59.22)	1197 (51.89)	183.13†	
Region				<0.01
Cixian	4021 (13.10)	257 (11.14)		
Feicheng	13,735 (44.74)	1064 (46.12)		
Linzhou	5887 (19.17)	650 (28.18)		
Yanting	3872 (12.61)	133 (5.76)		
Yangzhong	3186 (10.38)	203 (8.80)		
Education			−6.36‡	<0.01
Primary school	13,768 (44.84)	1215 (52.67)		
Junior high school	13,836 (45.07)	865 (37.49)		
Senior high school and above	3097 (10.09)	227 (9.84)		
Smoking			33.66†	<0.01
Yes	5864 (19.10)	555 (24.06)		
No	24,837 (80.90)	1752 (75.94)		
Alcohol			39.05†	<0.01
Yes	3833 (12.48)	392 (16.99)		
No	26,868 (87.52)	1915 (83.01)		
Water source			8.93†	<0.01
Natural water	12,783 (41.64)	1034 (44.82)		
Filtered water	17,918 (58.36)	1273 (55.18)		
Hot food			2.87†	0.090
≥1 day/week	5500 (17.91)	381 (16.51)		
<1 day/week	25,201 (82.09)	1926 (83.49)		
Vegetables (g/d)	305.10 ± 176.60	298.60 ± 174.90	1.68*	0.094
Fruits (g/d)	146.60 ± 81.80	144.70 ± 76.36	0.89*	0.371

Data are presented as *n* (%) or mean ± standard deviation. * *t* test. † Chi-square test. ‡ Wilcoxon test. BCH: Basal cell hyperplasia; EC: Esophageal cancer; HGIN: High-grade intraepithelial neoplasia; LGIN: Low-grade intraepithelial neoplasia. –:Not available.

Age, gender, region, education, smoking, alcohol, and water source, which were distributed differently between the positive and negative groups, were included in the logistic regression equation as confounding variables. The results showed that EC family history was significantly associated with positive esophageal diagnosis (OR = 1.66, 95% CI: 1.50–1.84, $P < 0.01$). Participants with positive family history of cancer or GEC had 1.49-fold (95% CI 1.36–1.62) or 1.52-fold (95% CI 1.38–1.67) higher risks of ECPL, respectively. Participants with single or multiple FDRs of positive EC family history had 1.65-fold (95% CI 1.47–1.84) or 1.93-fold (95% CI 1.46–2.54) higher risks

Table 2: Demographic characteristics and proportions of family history related factors in five high-risk areas in China.

Factors	Total	Cixian	Feicheng	Linzhou	Yanting	Yangzhong
Total	33,008	4278	14,799	6537	4005	3389
Age (years)	55.34 ± 7.50	54.83 ± 7.59	55.02 ± 7.46	55.95 ± 7.28	55.74 ± 7.81	55.71 ± 7.45
Gender						
Male	13,630 (41.29)	1743 (40.74)	6024 (40.71)	2375 (36.33)	2006 (50.09)	1482 (43.73)
Female	19,378 (58.71)	2535 (59.26)	8775 (59.29)	4162 (63.67)	1999 (49.91)	1907 (56.27)
FH of all cancers						
No	19,461 (58.96)	2482 (58.02)	9740 (65.82)	2607 (39.88)	2923 (72.98)	1709 (50.43)
Yes	13,547 (41.04)	1796 (41.98)	5059 (34.18)	3930 (60.12)	1082 (27.02)	1680 (49.57)
FH of GEC						
No	24,356 (73.79)	3288 (76.86)	11,555 (78.08)	4101 (62.74)	3355 (83.77)	2057 (60.70)
Yes	8652 (26.21)	990 (23.14)	3244 (21.92)	2436 (37.26)	650 (16.23)	1332 (39.30)
FH of EC						
No	26,865 (81.39)	3509 (82.02)	12,515 (84.57)	4801 (73.44)	3530 (88.14)	2510 (74.06)
Yes	6143 (18.61)	769 (17.98)	2284 (15.43)	1736 (26.56)	475 (11.86)	879 (25.94)
Number of FDR with EC history						
0	27,997 (84.82)	3619 (84.60)	12,865 (86.93)	5232 (80.04)	3570 (89.14)	2711 (79.99)
1	4510 (13.66)	570 (13.32)	1817 (12.28)	1120 (17.13)	410 (10.24)	593 (17.50)
≥2	501 (1.52)	89 (2.08)	117 (0.79)	185 (2.83)	25 (0.62)	85 (2.51)
Number of SDR with EC history						
0	31,647 (95.88)	4159 (97.22)	14,389 (97.23)	6011 (91.95)	3975 (99.25)	3113 (91.86)
1	1102 (3.34)	97 (2.27)	339 (2.29)	421 (6.44)	25 (0.63)	220 (6.49)
≥ 2	259 (0.78)	22 (0.51)	71 (0.48)	105 (1.61)	5 (0.12)	56 (1.65)

Data are presented as mean ± standard deviation or *n* (%). EC: Esophageal cancer; FH: Family history; FDR: First-degree relatives; GEC: Gastric and esophageal cancer; SD: Standard deviation; SDR: Second-degree relatives.

Table 3: Associations between family history related factors and esophageal pathologic diagnoses.

Factors	Normal/esophagitis/BCH	LGIN/HGIN/EC	OR (95% CI)*	*P* value
Family history of all cancers				
No	18,259 (59.47)	1202 (52.10)	Ref	–
Yes	12,442 (40.53)	1105 (47.90)	1.49 (1.36–1.62)	<0.01
Family history of GEC				
No	22,810 (74.30)	1546 (67.01)	Ref	–
Yes	7891 (25.70)	761 (32.99)	1.52 (1.38–1.67)	<0.01
Family history of EC				
No	25,146 (81.91)	1719 (74.51)	Ref	–
Yes	5555 (18.09)	588 (25.49)	1.66 (1.50–1.84)	<0.01
Number of FDR with EC history				
0	26,191 (85.31)	1806 (78.28)	Ref	–
1	4072 (13.26)	438 (18.99)	1.65 (1.47–1.84)	<0.01
≥ 2	438 (1.43)	63 (2.73)	1.93 (1.46–2.54)	<0.01
Number of SDR with EC history				
0	29,436 (95.88)	2211 (95.84)	Ref	–
1	1023 (3.33)	79 (3.42)	1.38 (1.09–1.75)	<0.01
≥2	242 (0.79)	17 (0.74)	1.29 (0.78–2.13)	0.324

Data are presented as *n* (%). Adjusting for age, gender, region, education, smoking, alcohol and water source. BCH: Basal cell hyperplasia; CI: Confidence interval; EC: Esophageal cancer; FDR: First-degree relatives; GEC: Gastric and esophageal cancer; HGIN: High-grade intraepithelial neoplasia; LGIN: Low-grade intraepithelial neoplasia; OR: Odds ratio; SDR: Second-degree relatives. –: Not available.

of ECPL, respectively. Participants with single SDR of positive EC family history had 1.38-fold (95% CI 1.09–1.75) higher risks of ECPL [Table 3].

Table 4 showed the associations between participants' diagnoses and the EC onset age of FDR. Compared with others, participants with FDR who developed EC before 35 years (OR = 4.05, 95% CI: 1.30–12.65, $P < 0.05$), 45 years (OR = 2.11, 95% CI: 1.37–3.25, $P < 0.01$) or 50 years of age (OR = 1.91, 95% CI: 1.44–2.54, $P < 0.01$) were more likely to be diagnosed as positive cases.

As the onset age of relatives decreased, the proportion of esophagitis/BCH in participants increased significantly and the proportion of normal esophagus decreased significantly [Figure 1]. In participants who had relatives with EC onset age < 50 years, the proportion of esophagitis/BCH was 32.62%. This proportion rose to 41.18% in those who had relatives with EC onset age < 35 years. In participants who had relatives with EC onset age < 50 years, the proportion of normal esophagus was 56.66%. This proportion decreased to 47.06% in those who had relatives with EC onset age < 35 years [Supplementary Table 1, http://links.lww.com/CM9/A899].

Discussion

We reported the associations between family history of cancer and ECPL using baseline data from five high-risk areas of China. We found that participants with positive family history of EC had higher risks of ECPL compared with family history of other types of cancer. And participants with FDRs who developed EC before 35 years of age had higher risks of ECPL. The proportion of positive family history varied significantly between high-risk areas.

EC is one of the main cancers in the world and its etiology is multifactorial and strongly population-dependent.[2] The epidemiologic and clinical characteristics of EC in China are different from those in Europe and America.[24] Incidence and mortality rates of EC are both high in China.[25] Provinces such as Henan, Hebei, and Shanxi which border on the Taihang Mountain belt in northern China are traditionally high-risk areas for EC.[11,26] These areas are also included in the Asian EC belt. Harsh mountain environment and conventional living habits are possible risk factors for EC in China.[27] What's more, obvious familial trends of EC in these high-risk areas indicate that genetic risk factors also play an important role in the EC oncogenesis.[10]

The Linxian General Population Trial was established to explore the influence of genetic risk factors on GEC, and 29,584 subjects were enrolled in 1984.[28] After 15 years'

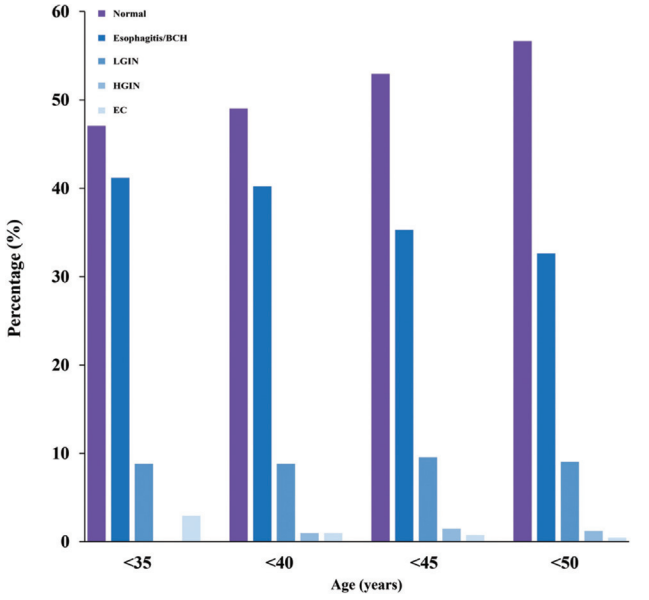

Figure 1: Distributions of esophageal pathologic diagnoses In participants with family history of early-onset EC, by relative's EC onset age. BCH: Basal cell hyperplasia; EC: Esophageal cancer; HGIN: High-grade intraepithelial neoplasia; LGIN: Low-grade intraepithelial neoplasia.

Table 4: Associations between number of FDR with early-onset EC and esophageal pathologic diagnoses, by FDR's EC onset age.

Number of FDR with early-onset EC	Normal/esophagitis/BCH	LGIN/HGIN/EC	OR (95% CI)*	*P* value
Onset age < 35 years				
0	30,683 (99.94)	2303 (99.83)	Ref	–
≥1	18 (0.06)	4 (0.17)	4.05 (1.30–12.65)	< 0.05
Onset age < 40 years				
0	30,633 (99.78)	2298 (99.61)	Ref	–
≥1	68 (0.22)	9 (0.39)	2.00 (0.97–4.13)	0.060
Onset age < 45 years				
0	30,511 (99.38)	2282 (98.92)	Ref	–
≥1	190 (0.62)	25 (1.08)	2.11 (1.37–3.25)	< 0.01
Onset age < 50 years				
0	30,221 (98.44)	2250 (97.53)	Ref	–
≥1	480 (1.56)	57 (2.47)	1.91 (1.44–2.54)	< 0.01

Data are presented as *n* (%). * Adjusting for age, gender, region, education, smoking, alcohol and water source. BCH: Basal cell hyperplasia; CI: Confidence interval; EC: Esophageal cancer; FDR: First-degree relatives; HGIN: High-grade intraepithelial neoplasia; LGIN: Low-grade intraepithelial neoplasia; OR: Odds ratio. –: Not available.

follow-up, associations between EC family history and EC (relative ratio [RR] = 1.42, 95% CI 1.29–1.56) were found. The RR for individuals with one EC FDR was 1.32 (95% CI 1.20–1.47). It increased to 1.89 (95% CI 1.59–2.25) for individuals with more than one FDR of EC;[28] Our study established similar results. The ORs of current study were relatively larger, which could partly be explained by the inclusion of LGIN and HGIN in the outcome.

Multiple case-control studies were conducted in recent years. Chen *et al*[17] conducted a study in Taixing areas in Jiangsu Province and observed a 1.85-fold risk of ESCC (95% CI 1.42–2.41) for participants with a positive EC family history among FDR. Wu *et al*[29] conducted a study in Ganyu and Dafeng areas in Jiangsu Province, and they reported that participants with positive cancer family history or positive EC family history among FDRs had 1.64-fold or 2.22-fold higher risks of EC, respectively. Gao *et al*[16] conducted a study in five places in Shanxi Province and observed that increased ESCC risk was associated with family history of any cancer (OR = 1.72, 95% CI 1.39–2.12), family history of any upper gastrointestinal cancer (OR = 2.28, 95% CI 1.77–2.95), and family history of EC (OR = 2.84, 95% CI 2.09–3.86). The OR values in our study were smaller than those of previous ones, which could partly be explained by the inclusion of population from multiple high-risk areas. However, the results of this study might be closer to the average level of high-risk areas in China.

For decades, high-risk areas had implemented a variety of prevention and control measures to reduce EC incidence and mortality, including living environment and lifestyle improvement programs, as well as population-based endoscopic screening programs. However, the genetic propensity of a population can hardly be changed by primary and secondary prevention measures. The results in this study were similar to those in previous studies, indicating that the effect of family history on abnormal esophageal pathology remained largely unchanged. The incidence of EC in Suining county was 20.34 per 100,000,[23] which was considered to be a non-high-risk area in China. The proportion of family history of EC in five high-risk areas ranged from 11.86% to 26.56%, which were all much higher than that in Suining (3.28%). These results indicated that genetic risk factors were still major threats for ECPL in high-risk areas. Further genetic epidemiologic research studies were needed to explore the unique etiology of EC in this population.

Based on the cancer registration data of the Hebei Fourth Hospital from 1973 to 1994, the researchers found that the onset age of cancer was associated with family history of cancer.[30] In this study, there was an association between the age of onset of relatives and ECPL. We also observed that the proportion of esophagitis/BCH was higher in individuals with early-onset EC relatives, indicating that the pathological progress of these individuals might be faster than that of the general population. In the follow-up stage of the NCEC study, we are going to explore the disease progression and intervention effect on individuals with early-onset EC relatives.

The main strengths of this study are the use of detailed family history information and pathologic diagnoses data of participants from five high-risk areas in China.[31] Although it is a cross-sectional study, the temporal association of risk factors and pathological outcomes is clearly established. Our research analyzes family history in detail, and all subjects have a clear pathological diagnosis. This research also has some limitations, including that the accuracy of information obtained by questionnaires may be compromised by recall bias and people in high-risk areas may be more likely to report positive family history. However, we can verify the disease status of most of the relatives except the fewer ones, who were diagnosed before the 1950s. These relatives who developed EC long ago were not diagnosed in secondary or higher hospitals, and the disease status cannot be confirmed by medical records.

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Conflicts of interest

None.

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