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RESEARCH REPORT

Earlier onset and multiple primaries in familial as opposed to sporadic esophageal cancer

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Abstract

AIM: To study the differences in onset age and multiple primary cancers between familial and sporadic esophageal squamous cell carcinoma (ESCC).

METHODS: The differences in onset age and multiple primary cancers were analyzed between ESCC patients with (n = 766) and without (n = 1776) a family history of the cancer. The cases analyzed constituted all consecutive patients who had undergone cure-intent surgery at the Department of Thoracic Surgery of the 4th Hospital of Hebei Medical University from January 1 1975 to December 31 1989. Because we also originally aimed to examine the difference in survival time, only older subjects with a long follow-up period were selected.

RESULTS: Overall, patients with ESCC and a positive family history of the cancer had a significantly younger age at onset and more multiple primary cancers than those without a positive family history (51.83 ± 8.39 *vs* 53.49 ± 8.23 years old, P = 0.000; 5.50% *vs* 1.70%, P = 0.000). Both of these differences were evident in subgroup analyses, however, no correlations were observed. While age at onset differed significantly by family history in males, smokers, and drinkers, the difference in multiple primary cancers by family history was significant in nonsmoking, nondrinking, and younger onset patients. In multivariate analysis, age over 50 years, tobacco smoking, and multiple primary cancers were found to be significant predictors of familial cancer: the corresponding OR (95%CI) and P-value were 0.974 (0.963-0.985) and 0.000; 1.271 (1.053-1.535) and 0.012; and 4.265 (2.535-7.176) and 0.000, respectively.

CONCLUSION: Patients with ESCC and a positive family history of the cancer had a significantly younger onset age and more multiple primary cancers than those without a positive family history. Sub-group analyses indicated that younger onset age may be due to the interaction of genetic predisposition and environmental hazards, and multiple primary cancers may only be due to genetic predisposition.

Key words: Esophageal squamous cell carcinoma; Familial cancer; Sporadic cancer; Age at onset; Synchronous primary carcinoma

Core tip: Patients with esophageal squamous cell carcinoma (ESCC) and a positive family history had a significantly younger onset age and more multiple primary cancers than those without a positive family history (51.83 ± 8.39 *vs* 53.49 ± 8.23 years old, P = 0.000; 5.50% *vs* 1.70%, P = 0.000). Both of these differences were evident in sub-group analyses, however, no correlations were observed. While age at onset differed significantly by family history in males, smokers, and drinkers, the difference in multiple primary cancers by family history was significant in nonsmoking, nondrinking, and younger onset patients. These results suggest a genetic component in ESCC. Furthermore, a younger onset age may be due to the interaction of genetic predisposition and environmental hazards, and

multiple primary cancers may only be due to genetic predisposition.

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INTRODUCTION

The incidence rates of most cancers increase with age, suggesting that cancers develop due to the accumulation of somatic mutations. If a germline mutation exists, however, fewer later life somatic mutations will be needed, and the cancer will develop at a younger age[1]. The "two-hit" hypothesis has been widely accepted to explain the occurrence of both familial and sporadic cancers by the inactivation of tumor-suppressor genes mechanism. In familial cancer, because the function of one allele of a crucial tumor suppressor gene has already been lost due to inheritance of a germline mutation (the first-hit, which theoretically is present in every cell), only inactivation of the remaining allele by a second-hit is necessary. For a sporadic cancer, however, both alleles have to be inactivated by two fateful somatic mutations: the chance is so small that under most circumstances only one cell is likely to be implicated[2,3]. Therefore, differences in age at onset and multiple primary cancers between cancer cases with or without a family history may suggest a genetic component in the etiology of the cancer[4-7].

In the Taihang mountain region in northern central China, the incidence rates of esophageal squamous cell carcinoma (ESCC) are the highest in the world, however, the risk factors for ESCC are not yet clear[8-16]. On analyzing a large surgical cohort at a field cancer center, we compared age of onset and multiple primary cancers in ESCC patients with and without a family history of the cancer. Our aim was to identify a genetic component using reliable clinicopathological data in a hospital-based surgical cohort.

MATERIALS AND METHODS

Ethics

The study was approved by the Institutional Ethics Review Board of the 4th Hospital of Hebei Medical University.

Subject selection

The high risk region and the Upper Gastrointestinal Cancer Center were previously described[4,5,7,9]. The data source was a hospital-based surgical registry of ESCC patients who had been operated on as early as October 1965. The subjects analyzed comprised all ESCC cases who had undergone cure-intent surgery in the Department of Thoracic Surgery of the 4th Affiliated Hospital of Hebei Medical University (also the Hebei Province Cancer Center) from January 1 1975 to December 31 1989. Because the 4th Hospital of Hebei Medical University used to be the only local cancer center capable of performing thoracic surgery and all surgical resections of esophageal cancer during that period were performed at the hospital, the cases analyzed comprised almost all incident resectable ESCC cases in the population.

Definition of family history and onset age

As ESCC and gastric cardia adenocarcinoma (GCA) have a common etiology in China[17-19] and have similar symptoms such as swallowing disturbance and substantial pain, a recalled family history was unable to distinguish between these two types of cancer when crucial documentation was missing[20,21]. Therefore, a positive family history was defined as at least one first- or two second-degree relatives diagnosed with ESCC/GCA. The family history was usually obtained by the surgeon on the first day of hospitalization. The onset age was the age at which the symptoms first appeared. Information on a positive family history of cancer included the site of cancer, blood relationship, when and where diagnosed, and vital status of the relative with cancer. In patients with a negative family history recalled at the time of hospitalization, if a first- or second-degree relative was subsequently diagnosed with ESCC or GCA, this question was routinely asked in the follow-up interview, and the information on family history was updated. Blood relationships were categorized as first, second, and third degree relatives.

Definition of synchronous multiple primary cancers

As ESCC and GCA in China share a susceptible genetic locus[17-19], we used not only multiple primary ESCCs, but also the coincidence of ESCC and GCA as evidence of genetic predisposition (a further explanation can be found in the discussion section). The presence of multiple primary cancers was investigated by reviewing the pathology report and slides of serial histological examinations. Evidence of a second primary cancer did not include high grade dysplasia or intraepithelial tumors as the diagnostic criteria were not consistent for these lesions during 1975-1989. With regard to the definition of second primaries, we used the following criteria: (1) both lesions exhibited definite malignant morphologic features and were not connected through the lymphatic system; and (2) both tumors were surrounded by intraepithelial tumors or dysplastic tissue. All 56 second primaries were discovered by endoscopy or barium X-ray examination during the out-clinic stage and were successfully resected.

Statistical analyses

Differences in demographic and clinicopathological distributions by family history were examined using the χ^2 test. A comparison of onset age between familial and sporadic cases was made using the Student's *t* test. A two-sided *P* value of less than 0.05 was considered statistically significant. To identify significant independent predic-

Table 1 Difference in age at onset in patients with esophageal squamous cell carcinomas with and without a family history of the cancer

	Positive family history		Negative family history		Differences	*P t*-test
	n (%)	Mean age (yr) ± SD (1)	*n* (%)	Mean age (yr) ± SD (2)	(1)-(2)	(1)-(2)
Total	766	51.83 ± 8.39	1776	53.49 ± 8.23	-1.66	0.000[b]
Sex						
Female	229 (33.80)	52.46 ± 7.91	600 (29.90)	53.48 ± 7.81	-1.02	0.100
Male	537 (66.20)	51.56 ± 8.58	1176 (70.10)	53.49 ± 8.44	-1.93	0.000[b]
Tobacco						
Nonsmoker	282 (36.80)	52.66 ± 8.03	739 (41.60)	53.63 ± 8.27	-0.98	0.090
Smoker	484 (63.20)	51.35 ± 8.56	1037 (58.40)	53.38 ± 8.13	-2.03	0.000[b]
Alcohol						
Nondrinker	480 (62.70)	52.10 ± 8.37	1200 (67.60)	53.38 ± 8.21	-1.29	0.004[a]
Drinker	286 (37.30)	51.38 ± 8.42	578 (32.40)	53.70 ± 8.28	-2.32	0.000[b]
Surgery year						
1975-1979	224 (29.20)	50.90 ± 8.21	376 (21.20)	52.36 ± 8.00	-1.46	0.034[a]
1980-1984	216 (28.20)	51.69 ± 8.58	545 (30.70)	52.95 ± 8.18	-1.26	0.050[a]
1985-1989	326 (42.60)	52.56 ± 8.34	855 (48.10)	54.32 ± 8.28	-1.76	0.001[b]
TNM						
$T_{is,1}N_0M_0$	34 (4.40)	50.94 ± 9.78	66 (3.70)	55.52 ± 7.24	-4.57	0.010[a]
$T_{2,3}N_0M_0$	422 (55.10)	51.64 ± 8.30	983 (55.30)	53.30 ± 8.37	-1.67	0.001[b]
$T_{2,3,4}N_1M_0$	310 (40.50)	52.19 ± 8.37	727 (40.90)	53.55 ± 8.10	-1.36	0.010[a]
Resection						
Exploratory	16 (2.10)	49.88 ± 8.16	28 (1.60)	52.57 ± 9.18	-2.70	0.340
R1 or R2	70 (9.10)	49.33 ± 10.00	152 (8.60)	54.73 ± 8.49	-5.40	0.000[b]
R0	680 (88.80)	52.13 ± 8.17	1596 (89.90)	53.38 ± 8.18	-1.25	0.001[b]

Positive family history *vs* negative family history, [a]$P < 0.05$, [b]$P < 0.01$.

tors of familial cancer, multivariate logistic analyses were performed in a backward manner to study the association between sex, age, smoking, drinking, presence of multiple primary cancers and the occurrence of multiple ESCC/GCA cases in the family. All calculations were performed using SPSS software version 13.0[22].

RESULTS

General demographic characteristics

The male:female ratio was 2.07:1 (1713/829) and the average age at onset was 52.89 years in males and 53.20 years in females. All 2542 ESCCs diagnosed in the 2524 patients were considered resectable before surgery, however, the actual resection rate was 89.5% (2276/2542). In general, no significant differences in demographic and clinicopathological characteristics were observed between the positive and negative family history groups (Table 1).

Of the 2542 ESCCs analyzed, 69.87% (1776/2542) developed in patients with no family history of the cancer and were regarded as sporadic; 30.13% (766/2542) were diagnosed in patients with a positive family history and were regarded as familial.

On reviewing the pathology reports and slides of serial histological examinations of the 2524 primary ESCC cases, 16 cases (0.63%) developed two primary ESCCs, 36 cases developed one ESCC and one GCA, two cases each developed two primary ESCCs as well as another primary GCA, and the remaining 2470 cases each developed a single primary ESCC. The 38 GCAs were taken as evidence of second primary cancer of ESCC, but were not included in the analyzed dataset of 2542 primary ESCCs.

Differences in age at onset in patients with ESCCs with and without a positive family history of the cancer

As shown in Table 1, the average age at onset of ESCCs (n = 766) with a positive family history was 51.83 years, significantly younger than that of 53.49 years for ESCCs with no family history (n = 1776, P = 0.000). Overall, the difference was 1.66 years, and the difference in subgroup analyses was significant for males, smokers, drinkers, non-drinkers, surgery during 1975-1979, 1980-1984, 1985-1989, tumor stage of $T_{is,1}N_0M_0$, $T_{2,3}N_0M_0$, $T_{2,3,4}N_1M_0$[23], complete resection (R_0) and partial resection (R_1/R_2) subgroups; but not significant for females, nonsmokers, and the exploratory surgery subgroup.

Patients with ESCCs and a positive family history are more likely to have multiple primary cancers

As shown in Table 2, 72 ESCCs had multiple primary cancers as they were associated with one or more primary ESCC/GCA in a single patient. The overall prevalence of multiple primary cancers was 2.8% (72/2542). The prevalence was 5.5% in the positive family history group compared with 1.7% in the negative family history group. The difference was significant (χ^2 = 27.80, P = 0.000).

When the sub-group analyses were performed, the difference in multiple primary cancer by family history persisted in all subgroups and was significant for males, females, younger onset age (under 55 years old), nonsmoking, non-drinking, $T_{2,3}N_0M_0$, and $T_{2,3,4}N_1M_0$ groups; but not significant for the older onset age (over 55 years old), smoking, drinking and $T_{is,1}N_0M_0$ groups.

Table 2 Difference in the prevalence of multiple primary esophageal squamous cell carcinoma/gastric cardia adenocarcinoma in patients with esophageal squamous cell carcinoma with and without a family history of the cancer

Classification	Family history	*n* (% of multiple primary cancer)	Total	χ^2	[a]*P*
Overall		72 (2.8)	2542		
	Negative family history	30 (1.7)	1776		
	Positive family history	42 (5.5)	766	27.80	0.000[b]
Sex					
Male	Negative family history	20 (1.7)	1176		
	Positive family history	27 (5.0)	537	15.30	0.000[b]
Female	Negative family history	10 (1.7)	600		
	Positive family history	15 (6.6)	229	13.52	0.000[b]
Age					
⩾ 55 yr	Negative family history	23 (2.6)	877		
	Positive family history	15 (5.0)	303	3.29	0.070
< 55 yr	Negative family history	7 (0.8)	899		
	Positive family history	27 (5.8)	463	32.06	0.000[b]
Tobacco					
Smoker	Negative family history	20 (1.9)	1037		
	Positive family history	1.8 (3.7)	484	3.63	0.060
Nonsmoker	Negative family history	10 (1.4)	739		
	Positive family history	24 (8.5)	282	32.48	0.000[b]
Alcohol					
Drinker	Negative family history	16 (2.8)	576		
	Positive family history	13 (4.5)	286	1.84	0.230
Nondrinker	Negative family history	14 (1.2)	1200		
	Positive family history	29 (6.0)	480	32.67	0.000[b]
TNM					
$T_{is,1}N_0M_0$	Negative family history	2 (3.0)	66		
	Positive family history	2 (5.9)	34	0.48	0.480
$T_{2,3}N_0M_0$	Negative family history	8 (0.8)	983		
	Positive family history	20 (4.7)	422	23.29	0.000[b]
$T_{2,3,4}N_1M_0$	Negative family history	20 (2.8)	727		
	Positive family history	20 (6.5)	310	8.03	0.010[b]

Positive family *vs* negative family, [a]$P < 0.05$, [b]$P < 0.01$.

Multivariate logistic regression analysis of factors associated with the occurrence of multiple ESCC/GCA cases in a family

When significant factors in univariate analysis as well as other related factors were entered into a binary logistic model, backward stepwise analysis removed insignificant variables step by step according to their contribution to the model. The order in which the insignificant variables were eliminated from the model was as follows: sex, primary tumor site, pre-surgical radiotherapy, and alcohol drinking. In the final model, age over 50 years, tobacco smoking, and multiple primary cancers were found to be significant independent predictors of familial cancer: the corresponding OR (95%CI) and *P*-value were 0.974 (0.963-0.985) and 0.000; 1.271 (1.053-1.535) and 0.012; and 4.265 (2.535-7.176) and 0.000, respectively (Table 3).

DISCUSSION

In the present analysis, we found that cases with a positive family history developed ESCC at a significantly younger age than those without such a family history. This was not due to earlier diagnosis as the stage distribution did not vary significantly between the two groups. We also found that a positive family history was significantly associated with a higher rate of multiple primary cancers. These observations suggest that this is a genetic component in ESCC. In Table 1, age at onset differed significantly by family history for males and smokers, but not for females and nonsmokers. Conversely, the age at diagnosis in males, smoking and alcoholic drinking cases was younger than that in females, non-smoking and non-drinking cases, respectively, when the family history was positive (51.56 *vs* 52.46, 51.35 *vs* 52.66, and 51.38 *vs* 52.10, respectively), but not observed when the family history was negative (53.49 *vs* 53.48, 53.38 *vs* 53.63, and 53.70 *vs* 53.38, respectively). These findings suggest a younger onset age of ESCC is due to the interaction between genetic and environmental risk factors (*i.e.*, only when both hazards are present).

Table 2 illustrates the different prevalences of multiple primary cancers by family history. What is interesting about this difference is that it was significant in the < 55 years, nonsmoking and nondrinking groups, but was non-significant in the > 55 years, smoking and drinking groups. The underlying reasons for this may be because age, smoking and drinking are established environmental risk factors for ESCC[10]. When these environmental risk factors do not exist, genetic predisposition must play a dominant role, therefore, significant differences in mul-

Table 3 Significant and independent predictors of familial esophageal squamous cell cancer by multivariate logistic analysis

Variables entered at each step	Regression coefficient	Standard error	Wald test value	*P*-value	OR	95%CI	
						Lower	Upper
Step 1							
Sex	-0.057	0.146	0.153	0.696	0.944	0.709	1.258
Age	-0.026	0.006	21.06	0.000[b]	0.975	0.964	0.985
Primary tumor site	0.235	0.349	0.451	0.502	0.791	0.399	1.568
Tobacco	0.153	0.140	1.195	0.274	1.165	0.886	1.532
Alcohol	0.113	0.112	1.019	0.313	1.120	0.899	1.396
Multiple cancer	1.427	0.267	28.49	0.000[b]	4.166	2.467	7.036
Presurgical radiotherapy	0.161	0.179	0.813	0.367	1.175	0.828	1.669
Constant	0.592	0.827	0.512	0.474	1.808		
Step 2							
Age	-0.026	0.006	21.068	0.000[b]	0.975	0.964	0.985
Primary tumor site	-0.241	0.349	0.479	0.489	0.786	0.397	1.556
Tobacco	0.187	0.108	3.001	0.083	1.206	0.967	1.491
Alcohol	0.123	0.110	1.250	0.264	1.131	0.912	1.402
Multiple cancer	1.427	0.267	28.497	0.000[b]	4.166	2.467	7.035
Presurgical radiotherapy	0.160	0.179	0.802	0.371	1.174	0.827	1.667
Constant	0.462	0.758	0.372	0.542	1.588		
Step 3							
Age	-0.026	0.006	21.311	0.000[b]	0.974	0.964	0.985
Tobacco	0.185	0.108	2.926	0.087	1.203	0.973	1.487
Alcohol	0.122	0.110	1.236	0.266	1.130	0.911	1.401
Multiple cancer	1.446	0.266	29.56	0.000[b]	4.246	2.521	7.152
Presurgical radiotherapy	0.157	0.179	0.773	0.379	1.170	0.824	1.662
Constant	-0.004	0.346	0.000	0.990	0.996		
Step 4							
Age	-0.026	0.006	22.395	0.000[b]	0.974	0.963	0.985
Tobacco	1.187	0.108	3.000	0.083	1.206	0.976	1.491
Alcohol	0.117	0.110	1.146	0.284	1.125	0.907	1.394
Multiple cancer	1.438	0.266	29.282	0.000[b]	4.213	2.502	7.092
Constant	0.037	0.343	0.011	0.915	1.037		
Step 5							
Age	-0.026	0.006	22.364	0.000[b]	0.974	0.963	0.985
Tobacco	0.240	0.096	6.245	0.012[a]	1.271	1.053	1.535
Multiple cancer	1.451	0.265	29.862	0.000[b]	4.265	2.535	7.176
Constant	0.108	0.337	0.104	0.747	1.114		

[a]$P < 0.05$, [b]$P < 0.01$ *vs* standard error.

tiple primary cancers by family history was only observed in the < 55 years, nonsmoking and nondrinking groups, but not in the > 55 years, smoking and drinking groups. This suggests multiple primary cancers, unlike age at diagnosis, reflects only genetic predisposition.

We used the coincidence of GCA as evidence of genetic predisposition for ESCC for the following reason: In China, GCA contrasts with esophagogastric junctional adenocarcinoma in the Western world, in that gastro-esophageal reflux disease or Barrett's esophagus is not a precursor[8]. Instead, GCA and ESCC have identical epidemiological distributions[17-21]. Molecularly, gene polymorphisms associated with elevated risks for both cancers were found in Hebei Province[13,14], and identical DNA alterations in the two cancers were reported in Henan Province[15,16]. These two provinces are located in the central area or the Taihang Mountain high-risk region. Recently, two genome-wide association studies of ESCC/GCA cases in China reported two susceptible loci, one at PLCE1 and the other (C20orf54) at 20p13, to be significantly associated with the risk of both cancers[17,18].

During surgery, the two cancers are often found to coincide in one patient: among the 2524 ESCC cases undergoing curative-intent surgery in the 4th Hospital of Hebei Medical University, the coincidence rate of ESCC and GCA was 1.5% (38/2524), twice as high as that of two primary ESCCs [0.7% (16/2524)].

In cancer genetics, a patient developing both an ESCC and a GCA may be less familial than a patient developing two primary ESCCs, but is certainly more familial than a single primary ESCC case.

Although epidemiological studies showed that a positive family history of UGIC increases the risk of both ESCC and GCA[20,21], the increased risk may be attributed to either common childhood household exposure or to genetic predisposition. As our results showed that younger onset age and multiple primary cancers are associated with familial as opposed to sporadic ESCC, we consider that the high risk associated with a positive family history is due to an inherited predisposition (for instance, the first-hit on a critical tumor suppressor gene) rather than childhood exposure to common household risk factors. This is because a background of inherited "first-hit", which theoretically exists in every cell, would make it more likely for independent tumors to develop in a tissue; in a sporadic case, however, the coincidence of

two mutations in one cell to inactivate both alleles of one tumor suppressor gene is so rare that under most circumstances only a single cell is likely to be involved, and thus the chance of two primary tumors is much less than it would be for a familial cancer case[23-25].

Although the difference in onset age between familial and sporadic cases was just 1.66 years, it is not merely a statistical advantage inherited in large sample sizes, because it was widely observed in all sub-classifications, significant in stage-specific subgroups according to the International Staging System[26], and more notably, in ESCCs with onset age < 55 years, family history was significantly associated with multiple primary cancers ($P = 0.000$), however, this association was not significant in the ≥ 55 years group ($P = 0.07$). This variation in strength by onset age was indicative of the effect of genetic predisposition.

Because all the double primary ESCC/GCA were clinically evident and surgically resected, these tumors only represent synchronous carcinomas detected clinically. If metachronous or intraepithelial tumors were included, much higher rates would have been observed.

In conclusion, we found significant differences in age at onset and multiple primary cancers between familial and sporadic ESCCs. Younger onset age results from genetic and environmental interaction, but multiple primary cancers may be more related to genetic predisposition.

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COMMENTS

Background

Although previous epidemiological studies have reported that a positive family history of esophageal cancer increases the risk of the cancer by 2- to 3-fold, the increased risk may be due to either common childhood household exposure or to genetic predisposition. If a younger onset age and more synchronous primary cancers were found to be associated with familial as opposed to sporadic esophageal squamous cell carcinoma (ESCC), the authors would be able to attribute the elevated risk associated with a positive family history to an inherited predisposition rather than childhood exposure to common household risk factors.

Research frontiers

According to the "two-hit story of tumor-suppressor gene in carcinogenesis", a background of inherited "first-hit" on a critical tumor suppressor gene, which theoretically exists in every cell of a tissue, would make it more likely for independent tumors to develop; in a sporadic case, however, the coincidence of two mutations to inactivate both alleles of a tumor suppressor gene is so rare that under most circumstances, only a single cell is likely to be involved, and thus the chance of two primary tumors is much less than it would be for a familial cancer case. Although many molecular findings have been suggested for the mechanism of genetic predisposition in ESCC, clinicopathological evidence is lacking.

Innovations and breakthroughs

For the first time, this study showed that ESCCs with a positive family history of the cancer have a significantly younger age at onset and more multiple primary cancers than those without a positive family history. This study clearly indicates that a genetic component exists in ESCC. It also demonstrates that clinicopathological characteristics of a cancer may be analyzed to identify evidence of genetic predisposition.

Applications

The molecular mechanism of genetic predisposition has not yet been determined for ESCC. By focusing attention on the onset age and number of primary cancers, as well as family history, it may be possible to pinpoint familial esophageal cancer cases and obtain specimens to study the exact molecular mechanism involved. In clinical practice, attention should be paid to familial cases to identify synchronous or metachronous second primary cancers.

Terminology

Like most cancers, ESCC exhibits considerable heterogeneity in etiology. Some are caused by the accumulation of somatic mutations brought about by environmental hazards, and others develop due to genetic predisposition. The former is known as sporadic cancer, while the latter is known as familial cancer. A family history of the cancer may be used to distinguish between the two cancer forms, but is not always reliable. Some familial cancer cases may lack a definite family history, under such circumstances, the onset age and second primary cancer may help to pinpoint a familial cancer.

Peer review

The authors have analyzed family history of cancer, as well as age at diagnosis and number of tumors, in a cohort of 2542 patients from Hebei Province with history of ESCC and gastric cardia adenocarcinoma. This topic is current, methods used and the results obtained in the paper are of good scientific value.

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