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ORIGINAL PAPER

Differences of onset age and survival rates in esophageal squamous cell carcinoma cases with and without family history of upper gastrointestinal cancer from a high-incidence area in North China

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Abstract
Background Gene expression analyses indicate that there are 152 genes of which the expression differs significantly in esophageal squamous cell carcinoma (ESCC) cases with positive as opposed to those with negative family history of upper gastrointestinal cancer (FHUGIC) in the high-incidence area for ESCC in northern China. However, the question as to whether there is any difference of onset age or survival rates in the familial and sporadic cases of ESCC in the area is unknown.
Aims To investigate the differences of onset age or survival rates in the familial and sporadic cases of ESCC for surgically treated ESCC patients from the high-incidence area.
Methods Retrospective analyses were performed on the clinicopathologic and survival data of ESCC cases ($N = 1715$) who had undergone surgery alone from 1985 to 1994 in Hebei Cancer Center, a provincial cancer center established primarily to treat esophageal cancer in the high-incidence area, to investigate the differences. All the patients had been native residents of the high-incidence area in northern China. Student's *t*-test was used to test the difference of onset ages, and Cox Proportional Hazard Model was used to examine the differences of survival rates in the familial and sporadic cases of ESCC.
Results Although the familial cases of ESCC had had a significantly earlier onset than the sporadic cases ($P < 0.00$), they experienced relatively lower survival rates than the sporadic cases after surgery. The differences of survival rates in the familial and sporadic cases were significant for patients above the age of 50 years ($P_{\text{Wald}} = 0.04$) and for the $T_{is,\ 1}\ N_0M_0$ group ($P_{\text{Wald}} = 0.04$), the differences were bigger for early-staged than for the later-stage groups, and the differences persisted when adjusted for or stratified by confounding factors such as sex, age (under versus above the age of 50 years), smoking, drinking, cancer segment location, surgery year (calendar year), stage (UICC 4th Ed, 1987), and Resection category. Overall, cases under the age of 50 years old showed a higher survival curve than cases above the age of 50 years old, and this was especially true for the familial case group where the difference was significant ($P_{\text{Wald}} = 0.03$).
Conclusion The findings suggest that the familial ESCC may develop earlier, and may have a poorer prognosis than the sporadic ESCC. Both earlier onset and poorer outcome may be important features for the familial as opposed to the sporadic cases of ESCC. The association between younger onset age and higher survival rates found for the familial cases may indicate some survival benefit for early discovery for people with positive FHUGIC in the high-incidence area.

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Keywords Esophageal squamous cell carcinoma · Family history of upper gastrointestinal cancer · Onset age · Survival curves · High-incidence area

Abbreviations

ESCC	Esophageal squamous cell carcinoma
FHUGIC	Family history of upper gastrointestinal cancer

Introduction

Epidemiological studies indicate that a positive family history of esophageal cancer increases the risk of esophageal squamous cell carcinoma (ESCC) in the high-incidence area in northern China [1–3]. A recent study confirmed that there were 152 genes of which the expression differed significantly in familial and sporadic cases of ESCC in the area [4]. In addition, molecular biological studies also find that the over expression of oncogenes such as MET, Fra-1, Neogenin, Id-1, and CDC25B etc. is related to the differentiation of ESCC [5–13], and hence to the prognosis of ESCC patients [14–26]. Based on the above evidences, we suspect that ESCC patients with a positive family history of upper gastrointestinal cancer (FHUGIC) may develop the cancer earlier, or may have lower survival rates than those without any FHUGIC. Herein, we report a retrospective analysis conducted to investigate the difference of onset age or survival rates in familial and sporadic cases of ESCC, and additionally to investigate the relationship between onset age and prognosis for a cohort of 1715 ESCC patients who have been native residents of a high-incidence area for ESCC in northern China and were treated by surgery alone in a single provincial Chinese cancer center.

Materials and methods

The high-incidence area

The high-incidence area for ESCC in northern China is a geographically mountainous area along the eastern side of the southern part of the Taihang Mountain. The southern part of Taihang Mountain extends from the south in Henan province towards the north while bordering the two provinces of Hebei and Shanxi province. The center of the high-incidence area for ESCC is the place where the three provinces of Henan, Hebei, and Shanxi meet. The 1715 ESCC cases analyzed have been native Hebei residents of this high-incidence area. The incidence rates from 1993 to 1997 for esophageal carcinoma in Cixian County which belongs to the Hebei province and is located at the center of the high-incidence area, were 133.9 and 105.0 per 100,000 for the male and female respectively [27]. The area also has a relatively high incidence for stomach carcinoma (with stomach cardia carcinoma included) compared with other areas in China. The incidence rate of stomach carcinoma for male and female in Cixian County were 55.9 and 28.0 per 100,000 respectively from 1993 to 1997 [27]. In a neighboring county called Shexian County, Hebei province, population-based cancer registration in 2000–2002 showed that the incidence rates for carcinoma of the esophagus, cardia and stomach constituted 80.8% of the incidence rate for all-site carcinoma for the male, and 75.9% for the female [28]. The Hebei province has 40 counties and approximately 30 million people living in the high-incidence area.

The Hebei Cancer Center

The Hebei Cancer Center, also the Fourth Affiliated Hospital of Hebei Medical University, consists of a Provincial Tumor Hospital and a Research Institute. The cancer center is located in the capital city of Shijiazhuang of Hebei province. The center was established in 1952 by the provincial government for research, education, and treatment of upper gastrointestinal cancer for the high-incidence area. From 1952 to June 30 2004, in total 18,149 cases of esophageal and cardia carcinoma underwent surgery in the center. Among them 55.7% of the cases (10,101/18,149) were native residents of the high-incidence area belonging to the Hebei province.

Subject selection

The data source is a hospital-based ESCC registry that was established in October 1965. Criteria for subjects selection were as following: (i) ESCC cases who underwent thoracic surgery in the Department of Thoracic Surgery of the Fourth Affiliated Hospital of Hebei Medical University from January 1 1985 to December 31 1994, and who had been native residents of the high-incidence area belonging to Hebei province, for the reason that we have obtained complete survival data only for patients of Hebei province. (ii) ESCC only, 221 cases with coexisting esophageal adenocarcinoma were excluded. (iii) Primary ESCC only, 52 cases with coexisting primary carcinoma other than the esophagus were excluded. (iv) Treated by surgery alone, 167 cases who had accepted multimodality

therapies such as preoperative radiotherapy ($N = 60$), preoperative chemotherapy ($N = 29$), and postoperative chemotherapy ($N = 78$) were excluded. (v) Cases died within 3 months after surgery were excluded from analyses ($N = 77$), and they were not significantly different in distribution of general and clinicopathologic characteristics from cases survived more than 3 months.

In the end 1715 Cases of ESCC were analyzed. They have been followed up biannually with systemic examination, biochemical test, chest radiography, sonography etc. at least for 10 years after surgery to the endpoint for analysis on August 15 2003. A complete event was assigned for the survival status if the patient had died directly or indirectly of esophageal cancer. Otherwise the survival time was treated as a censored value. The survival information of each of the 1715 patients had been specially verified again for the analysis. The Institutional Ethics Review Board of the Hebei Cancer Institute in Hebei Medical University approved the study.

Definition of FHUGIC, and familial versus sporadic cases

The thoracic surgeon in charge of the patient obtained detailed information for onset age and family history of cancer personally usually on the first day of hospitalization. The onset age was calculated by the date on which the disease manifested in symptoms such as swallowing disturbance, substernal pain, etc. minus the patient's date of birth. Information for family history of cancer including the site of carcinoma, blood relationship with the proband, diagnosed when and where, and vital status for any relative who had been diagnosed with cancer was based on recalling by the proband, and checked by the proband's closest relatives. Blood relationship with the proband was categorized as first, second, and third degree relatives. Because carcinoma of the esophageal, cardiac and stomach are prevalent cancers which make up roughly 70–80% of all-site carcinoma in the high-incidence area, and because the three upper gastrointestinal cancers were usually undistinguishable due to the usual missing of pathological record for a relative recalled as having been affected with any of the three prevalent cancer, We combined family history of the esophageal, cardia, and stomach cancer into one variable as FHUGIC. Among the 1715 cases of ESCC, 72.2% (1238/1715) were with negative FHUGIC, they were regarded as the sporadic cases; and 27.8% (477/1715) were with positive FHUGIC, and they were regarded as the familial cases. Among the familial case group, 70.0% of the cases (334/477) recalled their parents, 12.4% (59/477) recalled their siblings, 1 case recalled her son, 15.3% (73/477) recalled their uncles or aunts, and 2.1% (10/477) recalled their third degree relatives as having been diagnosed with upper gastrointestinal cancer.

Statistical analyses

Survival analyses were performed using the Kaplan Meier method. Differences of clinicopathologic variables among groups were calculated using Chi-square Test. The differences of onset age in familial and sporadic cases were tested using Student's *t*-test. A two-sided P value of less than 0.05 was considered as statistically significant. Test of significance for a prognostic factor with sex, age (under versus above the age of 50 years), FHUGIC, smoking, drinking, cancer segment location, surgery year (calendar year), TNM stage (4th Ed, 1987), and resection category adjusted accordingly were performed with Wald Test within the Cox Proportional Hazard Model. All the calculations were performed using SPSS software version 10.0 [29].

Results

Distribution of characteristics by FHUGIC and onset age

As shown in Table 1, among cases with onset above the age of 50 years, a significantly larger proportion of the familial cases underwent surgery during the earlier 5-year period from 1985 to 1989 than sporadic cases (51.5% vs. 45.0%, $P < 0.05$). Among cases with onset under the age of 50 years, a larger proportion of the familial cases were in stage $T_{is,1}N_0M_0$ than the sporadic cases (5.1 % Vs 2.3%, $P = 0.17$). In addition, among the sporadic cases, a significantly larger proportion of cases with onset above the age of 50 years were found to have ESCC located in the lower third segment than cases with onset under the age of 50 years (30.4% vs. 21.6%, $P = 0.00$). For other factors such as sex, smoking, drinking, and resection category, no meaningful difference in distribution was observed.

Differences of onset age in the familial and sporadic cases

As shown in Table 2, the familial cases on the average had a significantly earlier onset than the sporadic cases. For the total, the difference of onset age in familial and sporadic cases was 1.4 year, and the differences were apparent for most subgroups, including male and

Table 1 Characteristic distribution of 1715 cases of surgically treated ESCC by FHUGIC and by onset age of under or above the age of 50 years

	Without FHUGIC (N = 1238)		With FHUGIC (N = 477)		Two-sided P-value by chi-square test			
	<50 (N = 398) No (%) (1)	≥50 (N = 840) No (%) (2)	<50 (N = 176) No (%) (3)	≥50 (N = 301) No (%) (4)	(1) vs. (2)	(3) vs. (4)	(1) vs. (3)	(2) vs. (4)
Surgery year					0.29	0.50	0.99	0.05*
1985–1989	192(48.2)	378(45.0)	85(48.3)	155(51.5)				
1990–1994	206(51.8)	462(55.0)	91(51.7)	146(48.5)				
Sex					0.47	0.75	0.49	0.26
Male	275(69.1)	563(67.0)	129(72.2)	213(70.8)				
Female	123(30.9)	277(33.0)	49(27.8)	88(29.2)				
Smoking					0.45	0.62	0.86	0.40
Nonsmoker	152(38.2)	321(38.2)	63(35.8)	102(33.9)				
Smoker	229(57.5)	469(55.8)	105(59.7)	179(59.5)				
Missing	17(4.3)	50(6.0)	8(4.5)	20(6.6)				
Drinking					0.29	0.61	0.82	0.27
Nondrinker	219(55.0)	446(53.1)	93(52.8)	145(48.2)				
Drinker	146(36.7)	300(35.7)	66(37.5)	123(40.9)				
Missing	33(8.3)	94(11.2)	17(9.7)	33(11.0)				
Site					0.00**	0.65	0.83	0.62
Upper and cervical	11(2.8)	22(2.6)	5(2.8)	7(2.3)				
Middle	301(75.6)	563(67.0)	129(73.3)	211(70.1)				
Low	86(21.6)	255(30.4)	42(23.9)	83(27.6)				
TNM stage					0.43	0.29	0.17	0.75
$T_{is,1}N_0M_0$	9(2.3)	30(3.6)	9(5.1)	8(2.7)				
$T_{2,3}N_0M_0$	217(54.5)	441(52.5)	97(55.1)	160(53.2)				
$T_{2,3,4}N_1M_0$	172(43.2)	369(43.9)	70(39.8)	133(44.2)				
Resection category					0.61	0.04*	0.29	0.17
Exploratory	2(0.5)	5(0.6)	2(1.1)	1(0.3)				
R_1 or R_2	28(7.0)	45(5.4)	9(5.1)	18(6.0)				
R_0	344(86.4)	730(86.9)	148(84.1)	271(90.0)				
Missing	24(6.0)	60(7.1)	17(9.7)	11(3.7)				

*P < 0.05; **P < 0.01

female, the earlier or latter 5-year period of surgery time (1985–1989 or 1990–1994), smoking, drinking, TNM stages, resection category, and even in subgroups with missing value for classification. Still interestingly, the differences of onset age in familial and sporadic cases seemed to be stage related; for instance, the differences were significant for $T_{is,1}$ N_0M_0, $T_{2,3}N_0M_0$, or the alternative resection category of R_0 subgroups, but not significant for $T_{2,3,4}N_1M_0$, and the alternative resection categories of R_1, R_2 or the palliative subgroups.

Differences of survival rates in the familial and sporadic cases

Although the familial cases had been diagnosed and operated significantly younger than the sporadic cases, they generally had lower survival rates than the sporadic cases (over all, the adjusted P_{Wald} = 0.35, as shown by the 1st of Fig. 1). The differences of survival rates in the familial and sporadic cases reached significant level for above the age of 50 years group (Adjusted P_{Wald} = 0.04, shown as the 2nd in Fig. 1), and for the $T_{is,1}$ N_0M_0 group (Adjusted P_{Wald} = 0.04, shown as the 3rd in Fig. 1). The differences were obvious for most subgroups, similar to that observed for the $T_{2,3}$ N_0M_0 group as shown by the 4th in Fig. 1 (Adjusted P_{Wald} = 0.40). Liking the differences of onset age in familial and sporadic cases, the differences of survival rates also seemed to be stage-related; as shown by the 3rd, 4th, and 5th in Fig. 1, the differences were significant for the $T_{is,1}$ N_0M_0, obvious for the $T_{2,3}N_0M_0$, but disappeared for the $T_{2,3,4}N_1M_0$ cases.

The differences of survival rates in familial and sporadic cases were significant not only for the above the age of 50 years and the $T_{is,1}$ N_0M_0 group separately (As shown by the 2nd and 3rd of Fig. 1), but held out for each stage above the age of 50 years (as shown by the 1st, 2nd and 3rd of Fig. 2), indicating the poorer outcome for the familial than for the sporadic cases observed for above the age of 50 years group only (not for under the age of 50 years group) was not brought about by unbalanced stage distribution between the

Table 2 Differences of onset age in cases without and with FHUGIC for 1715 cases of surgically treated ESCC

	Without FHUGIC (N = 1238)		With FHUGIC (N = 477)		Difference in onset age (2)–(4)	Two-sided P for (2)–(4) By Student's t-test
	No. (%) (1)	Onset age (Mean ± SD) (2)	No. (%) (3)	Onset age (mean ± SD) (4)		
Total	1238	53.2 ± 8.2	477	51.8 ± 8.3	+1.4	0.00**
Sex						
Males	838	53.2 ± 8.3	340	51.7 ± 8.5	+1.5	0.00**
Females	400	53.3 ± 8.1	137	52.2 ± 7.8	+1.1	0.16
Onset age						
< 50	398	43.6 ± 4.3	176	43.2 ± 5.1	+0.4	0.38
≥50	840	57.8 ± 5.1	301	56.9 ± 5.1	+0.9	0.01**
Smoking						
Nonsmoker	473	53.5 ± 8.5	165	52.6 ± 8.2	+0.9	0.23
Smoker	698	53.1 ± 8.2	284	51.2 ± 8.5	+1.9	0.00**
Missing	67	52.6 ± 6.3	28	53.3 ± 7.4	–0.7	0.65
Drinking						
Nondrinker	665	53.4 ± 8.5	238	52.1 ± 8.4	+1.3	0.05*
Drinker	446	53.1 ± 8.1	189	51.5 ± 8.3	+1.6	0.02*
Missing	127	52.7 ± 7.6	50	51.5 ± 8.3	+1.2	0.40
Surgery year						
1985–1989	570	52.6 ± 8.2	240	51.2 ± 8.2.	+1.4	0.03*
1990–1994	668	53.8 ± 8.2	237	52.5 ± 8.4	+1.3	0.04*
Cancer site						
Upper and cervical	33	54.8 ± 8.6	12	50.3 ± 7.9	+4.5	0.12
Middle third	864	52.6 ± 8.2	340	51.4 ± 8.3	+1.2	0.03*
Low third	341	54.8 ± 8.2	125	53.1 ± 8.5	+1.7	0.05*
TNM stage						
$T_{is,1}N_0M_0$	39	55.1 ± 7.1	17	50.3 ± 10.7	+4.8	0.05*
$T_{2,3}N_0M_0$	658	53.1 ± 8.3	257	51.6 ± 8.5	+1.5	0.01**
$T_{2,3,4}N_1M_0$	541	53.2 ± 8.3	203	52.2 ± 7.9	+1.0	0.14
Resection category						
Exploratory	7	51.9 ± 8.2	3	48.7 ± 5.7	+3.2	0.56
R_1 or R_2	73	53.0 ± 8.9	27	52.6 ± 7.7	+0.4	0.84
R_0	1074	53.2 ± 8.1	419	52.1 ± 8.4	+1.1	0.02*
Missing	84	53.8 ± 9.3	28	47.6 ± 7.1	+6.2	0.00**

*$P < 0.05$; **$P < 0.01$

familial and sporadic cases for the reason that when analysis was restricted to older patients only, the familial cases might be more likely to be later-staged than the sporadic cases.

The relationship of onset age with survival rates

As shown by the 1st of Fig. 3, Overall, ESCC cases under the age of 50 years old experienced a relatively better survival than those above the age of 50 years old (Adjusted $P_{Wald} = 0.18$), but the relationship was inconsistent between the familial and sporadic groups; among the sporadic group, there was no difference of survival rates in cases under and above the age of 50 years (Adjusted $P_{Wald} = 0.65$, as shown by the 2nd in Fig. 3); but among the familial case group, cases under the age of 50 years old had survival rates significantly higher than that of cases above the age of 50 years. (Adjusted $P_{Wald} = 0.03$, shown by the 3rd of Fig. 3).

Discussion

In 1999, Hu reported a significant difference of Allelic loss in ESCC cases with and without FHUGIC [30]. Recently, gene expression analysis demonstrated that there were 152 genes of which the expression differed significantly in ESCC cases with positive as opposed to those with negative FHUGIC [4]. The two studies had researched by samples taken from the same high-incidence area as the present analysis. The findings of the two studies suggest that the genetic background of familial ESCC patients is different from that of sporadic cases. The present analysis found that familial cases had a significantly earlier onset than the sporadic cases, suggesting that a positive FHUGIC brings a higher risk of developing ESCC. This finding epidemiologically supports the results of the two earlier molecular studies.

A series of researches report that genes such as Mina 53, Eph A2, nm23-H1, Caspase-3 etc are related

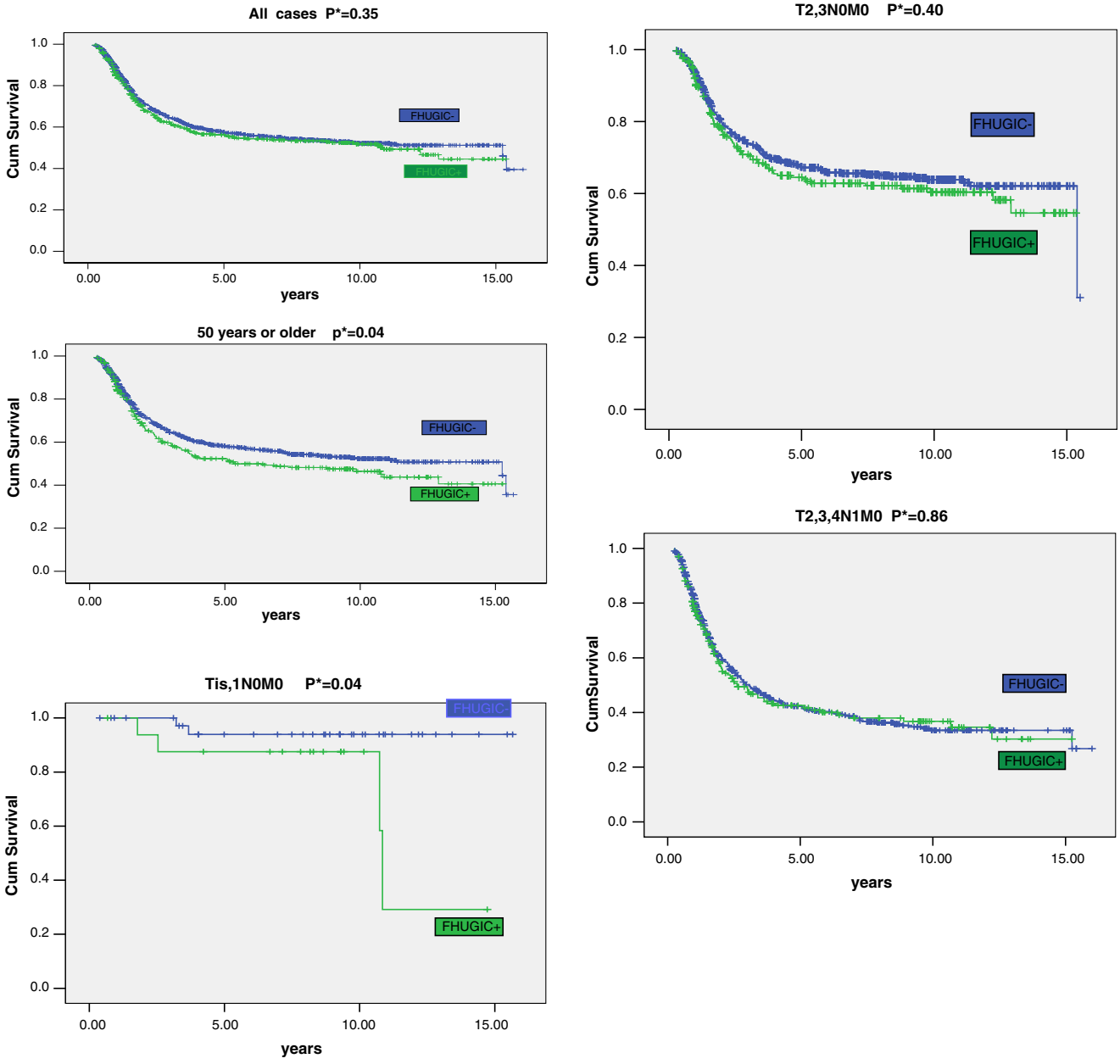

Fig. 1 Differences of survival curves in ESCC cases with and without FHUGIC for all cases combined, for cases with onset above the age of 50 years, and for cases of $T_{is,1}N_0M_0$, $T_{2,3}N_0M_0$, and $T_{2,3,4}N_1M_0$ respectively. *Probability adjusted for sex, onset age (above or under the age of 50 years), smoking, drinking, cancer segment location, surgery year (calendar year), stage (UICC), and resection category accordingly by Wald Test within the Cox Proportional Hazard Model

to the prognosis of ESCC [14–26]. Our analysis found that although the familial cases of ESCC had a significantly younger onset age than the sporadic cases, they otherwise experienced relatively lower survival rates; The differences were significant for patients above the age of 50 years old and for the $T_{is,1}N_0M_0$ group, apparent in most of the relatively large numbered subgroups, and larger in earlier-staged than in later-staged groups. Adjustment for confounding factors such as sex, age, smoking, drinking, cancer location, surgery year, resection category, and UICC stage by Cox regression had not altered the results of significance tests. These findings suggest that the genetic background, as reflected by FHUGIC, not only determines the risk of ESCC development, but it may also has some potential value of prognosis. To our knowledge, this analysis has been the first to report an obvious difference of survival rates in familial and sporadic cases by a large group of surgically treated ESCC followed-up over 10 years.

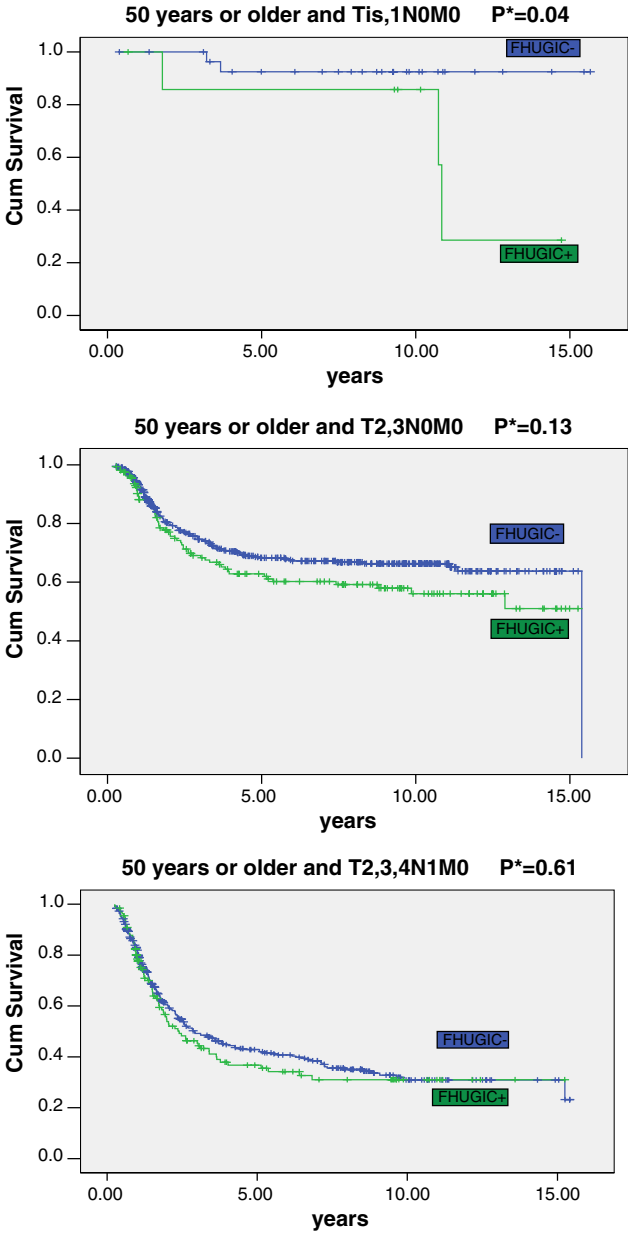

Fig. 2 Differences of survival curves in ESCC cases with and without FHUGIC for cases with onset above the age of 50 years and in $T_{is,1}N_0M_0$, $T_{2,3}N_0M_0$, and $T_{2,3,4}N_1M_0$ respectively. *Probability adjusted for sex, smoking, drinking, cancer segment location, surgery year (calendar year), and resection category by Wald Test within the Cox Proportional Hazard Model

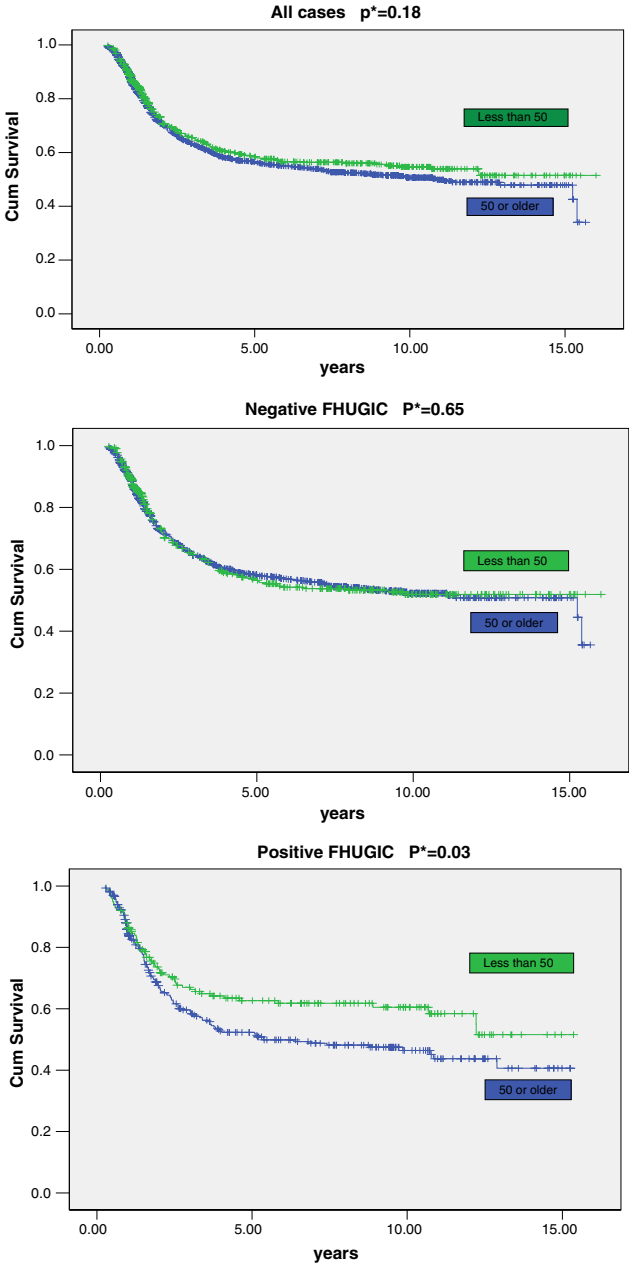

Fig. 3 Differences of survival curves in ESCC cases with onset under and above the age of 50 years for all cases, for the negative FHUGIC group, and for the positive FHUGIC group. *Probability adjusted for sex, FHUGIC, smoking, drinking, cancer segment location, surgery year (calendar year), TNM stage, and resection category by Wald Test within the Cox Proportional Hazard Model

Since subjects analyzed by us were one hospital based and restricted to operated cases only (with patients too late for surgery and undergoing multimodality therapy excluded), the problem of selection bias had ever aroused much consideration. Ideally an investigation of the differences of onset age in familial and sporadic cases should be made with all incident cases in a population-based registry. But unfortunately, our population-based cancer registries in the high-incidence area had not registered information on family history of cancer until recently; and hospital-based registries have not included late-staged nonresectable cases. To investigate the degree of selection bias, we made a survey in 2003 on all the 620 cases who had been registered as ESCC in Shexian County from 2000 to 2001. The results found 285 cases (46.0%) with

positive FHUGIC, 271 cases (43.7%) with negative FHUGIC, 14 cases (2.3%) with positive family history for other malignances, and 50 cases (8.1%) unable to recall a definite answer. The onset age for the above four groups were 59.1 ± 8.1, 61.1 ± 9.4, 61.4 ± 6.3, 60.0 ± 8.6 respectively. The only significant difference of onset age observed was that between the positive and the negative FHUGIC group ($P = 0.03$). Such a result encouraged us to continually use the hospital-based dataset for survival difference analyses.

Since there are steady improvements in surgical results for esophageal cancer over time, the results of survival analyses for familial and sporadic cases may easily be biased if their surgery time is incomparable. As mentioned at the beginning of the Results section, among cases with onset above the age of 50 years, a significantly less proportion of familial cases underwent surgery during the latter 5-year period from 1990 to 1994 than the sporadic cases (48.5% vs. 55.0%, $P < 0.05$). We had suspected that this might have produced the false lower survival curve for the familial than for the sporadic cases. To exclude the suspicion, we plotted the survival curves for the familial versus the sporadic cases for each surgery year from 1985 to 1994 with Kaplan–Meier method; It was found that the survival curves showed no difference in position for the familial and sporadic cases for 2 year of 1985 and 1993; for 1992 showed a reversed pattern; as for the other 7 years, consistent lower survival curves were observed for the familial than for the sporadic cases, suggesting that the lower survival curve observed for the familial than for the sporadic among the group of cases above the age of 50 years had not been produced by the confounding effect of incomparable surgery time. Still interestingly, it was found during the process that the yearly difference of survival rates in the familial and sporadic cases seemed to be positively correlated with the yearly difference of onset age; for example, from 1986 to 1991, the familial cases had onset age on the average younger than the sporadic cases, and the corresponding survival curves for these 6 years showed a consistent lower position for familial cases than for the sporadic cases; for the 2 year of 1985 and 1993, the difference of onset age were slight or near zero, and the survival curves also showed no difference in position; for the only year of 1992, the familial cases had onset unusually later than the sporadic cases ($P < 0.15$), and the survival curves also showed a contrary pattern to common years. This concurrent appearance of an earlier onset and a lower survival curve for the familial than for the sporadic cases may prove the two evidences mutually supporting each other, and both reflecting the malignancy of familial ESCC as compared with the sporadic type.

It has been commonly thought that ESCC cases with a younger onset age might be more aggressive than the older cases, and therefore might have a poorer survival than the older cases [31, 32]. However, results of present analysis suggest that overall, cases under the age of 50 years still have a favorable outcome than those above the age of 50 years old. This is especially true for the familial group. Here the meaningful suggestion is: in the high-incidence area in northern China, it has been reported that 25.4% of the fathers, 17.62% of the mothers, 12.39% of the brothers, and 9.42% of the sisters of esophageal cancer patients had been or would be diagnosed with esophageal cancer [2]. The percent of patients with positive family history of esophageal cancer for hospital based esophageal cancer cases was 22.1% [1]. Considering the number of people with positive FHUGIC in the high-incidence area is very large [3, 27, 28], an association of younger age with better survival for them is noteworthy, it may suggest a survival benefit for early discovery. The lack of difference in survival between the younger and the older cases for the sporadic group may be due to the different cancer-location distribution between them as mentioned in the end of the first part of the Result section for the reason that the prognosis of upper thoracic esophageal carcinoma is often worse than that in the distal esophagus [33].

The study also has some other strengths worth mentioning; first, the fact that a significantly earlier onset was observed for the familial than for the sporadic cases of ESCC suggests that the quality of the dataset is reasonable. Second, although we had survival data for ESCC patients after surgery since 1966, we restricted analyses to a minimum period from 1985 to 1994 to control for confounding over time. Third, the fact that all the cases analyzed had been determined by the same department to be potential candidates for radical resection, and the patients had come from families rich enough to afford the cost of thoracic surgery in Hebei Cancer Center has helped to balance the familial and sporadic cases on stage and socio-economical background. In addition, the fact that all cases were operated by the same a dozen of thoracic surgeons in the same department following a standard for ESCC resection for many years also has helped to ensure comparability in medical quality between the familial and sporadic cases. During analyses, full adjustment was made with confounding factors such as age, sex, FHUGIC, smoking, drinking, cancer location, TNM stage, resection category, and surgery year by the

Cox Proportional Hazard Model. Carefully stratified analyses as reflected by Fig. 2 have been conducted to verify the results.

In conclusion, we found that familial cases of ESCC have onset significantly earlier than sporadic cases, and despite being younger at onset, they have relatively lower survival rates than the sporadic cases, the differences in survival are significant for above the age of 50 years group, more significant for earlier-staged than for later-staged groups, and are not brought about by confounding effects. These results indicate that the familial ESCC cases not only develop the cancer earlier, but their cancer cells may be more aggressive than that of the sporadic cases. Additionally, a significantly higher survival curve observed for cases under the age of 50 years than for cases above the age of 50 years among the familial case group may indicate some survival benefit for early discovery for people with positive FHUGIC in the high-incidence area.

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