

Familial Aggregation of Oesophageal Cancer in a High Incidence Area in China

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Background. The high incidence of oesophageal cancer in northern China is attributed predominantly to environmental factors. The role of genetic factors has not been extensively studied.

Methods. Our aim was to study familial aggregation of oesophageal cancer in pedigrees from a defined population base in a high incidence area in China and to quantify the risk associated with different first degree relatives using different analytical approaches. Detailed data on family members of three successive generations and the occurrence of oesophageal and other cancers in family members were collected from a population-based series of 244 oesophageal cancer cases which occurred between 1987 and mid-1992 in Huixian County, Henan.

Results. Compared to expected rates, the standardized mortality ratio (SMR) of oesophageal cancer among first degree relatives of oesophageal cancer patients was 2.4 (2.2 in male and 2.7 in female relatives). The corresponding SMR for first and second degree relatives were 1.6 and 2.2. The null hypothesis of 'no familial aggregation' was rejected using Tarone's one-sided score test for binomial distributions indicating some evidence for clustering within families. To account for variance due to between-pairs correlation and family and/or individual specific variables, we fitted a series of regression models using a Generalized Estimation Equations (GEE) approach. The pairwise odds ratios were 2.3 for parent-parent, 1.9 for sib-parent and 1.1 for sib-sib, adjusted for sex, age and sex of index case.

Discussion. The existence of familial aggregation of oesophageal cancer in the study population was confirmed using different analyses and a two- to threefold increased risk was found for first degree relatives. The clear association of disease between parent and sib provides some indication of a genetic component. The pairwise association between parents but not between sibs suggests that environmental factors have a stronger action after childhood.

Keywords: family, genetic analysis, odds ratio, regression models

The large geographical variation in oesophageal cancer incidence was always taken to be an indication of strong environmental factors being involved in the aetiology of oesophageal cancer. Extended epidemiological studies in high incidence areas such as northern Iran, northern China, Kashmir and South Africa as well as in northern France provide evidence that exposure to tobacco-related carcinogens and/or diet-related N-nitroso compounds in parallel with nutritional deficiency are the most important determinants of the disease.^{1–4}

In China, a role of familial factors in cancer of the oesophagus was suggested very early by the observation of a positive family history in a higher percentage

of cases (22.1%) than of hospital controls (5.5%).⁵ Two subsequent epidemiological case-control studies conducted in high incidence areas for oesophageal cancer in China found a positive association between the family history of oesophageal cancer and the risk for oesophageal cancer.^{6,7} In Linxian the risk was increased by 70% among those whose parents had oesophageal or stomach cancer while only 20% among those whose spouses had such cancers, suggesting that exposures early in life and/or genetic factors may be involved.⁶ In the study conducted in Shanxi province, the relative risk of family history was 2.0 for all blood relatives but 6.0 and 4.0 for brothers or sisters, respectively.⁷

Familial aggregation of oesophageal cancer was investigated over many years in Yangcheng county, Shanxi province, and a follow-up study showed a higher rate of new oesophageal cancer cases in families with a history of oesophageal cancer than in those without.^{8,9} Furthermore, evidence of genetic factors in the aetiology

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of oesophageal cancer in Huixian was provided by segregation analysis on 221 high-risk nuclear families in Linxian which indicated an autosomal recessive Mendelian inheritance.¹⁰

In an epidemiological study of precursor lesions of oesophageal cancer among people aged 15–26 years conducted in a high incidence area of China, we found that the prevalence of oesophagitis was strongly associated with both a concomitant prevalence of oesophagitis among siblings (odds ratio [OR] = 4.4) and a family history of oesophageal cancer (OR = 1.8), after accounting for environmental factors.¹¹ These findings suggest that chronic oesophagitis is involved in the natural history of oesophageal cancer and that there may be a common susceptibility for both chronic oesophagitis as a precursor state and for the development of oesophageal cancer. Therefore, it appeared warranted to conduct further studies in this population to investigate genetic susceptibility in the development of oesophageal cancer.

This study was undertaken to confirm the existence of familial aggregation among oesophageal cancer cases in Huixian county and to quantify the risk associated with different first degree relatives by employing different types of analyses. In this paper we present results using methods of analysis suitable for assessing familial aggregation in general, without considering specific genetic hypothesis.

MATERIALS AND METHODS

The population base selected was one commune, Mengzhuang, with about 47 000 inhabitants in 27 villages in Huixian county, Henan province. A mortality survey in 1974–1976 showed that Huixian county had an oesophageal cancer age-adjusted mortality of 120.9 per 100 000 for males and 68.0 per 100 000 for females.¹² In comparison the corresponding rates for the total Henan province were 47.2 and 30.2, respectively. Incident oesophageal cancer cases (including cardia cancer) were identified from the registration books of the village doctors in Mengzhuang for the past 5½ years between 1987 and June of 1992 to enrol about 250 cases. All diagnoses of the index cases were confirmed by x-ray and/or histology. The village doctors were trained to collect family data through interviews using a standardized family questionnaire. Detailed data on the number of family members in four successive generations, including grandparents of the index case, his/her parents, uncles and aunts, and their spouses and children, siblings and their spouses, and offspring were collected. Information concerning the vital status of all members of the pedigrees and the occurrence of oesophageal and other

cancers was obtained in 1992. Interviews were performed in the home of the index cases and the source of the family information was the index oesophageal cancer case, if still alive, or the next-of-kin, if the index case was deceased. Other family members who were better informed about the larger family structure were sometimes consulted. The registration books of the village doctors were used to validate the reporting of oesophageal cancer occurrence, however, most of the oesophageal cancer deaths occurring more than 10 years earlier were solely based on reporting by recall. No further attempt was made to confirm the diagnoses. The data were manually edited in Huixian; and then coded and verified in Germany.

Data were more complete from families of male index cases than female index cases because of the Chinese custom of women marrying out of the village and often losing contact with their parents after marriage. Birth year or current age/age at death was almost complete for first degree relatives. However, it was often unknown for second degree relatives; it was unknown for 62.5% of the grandfathers, 65.5% of the grandmothers and 19.4% of uncles and 29.7% of aunts. There was an extreme deficit of oesophageal cancer cases among grandfathers and grandmothers which was most likely due to underreporting. There may also have been a survivorship bias if affected grandparents died earlier on average and thus dates of birth and death are missing. The information with regard to date of birth, date of death and cause of death was not considered sufficiently reliable for the grandparents. Therefore, in the statistical analyses presented, grandparents were excluded. Data for aunts and uncles were used for some of the analysis.

Statistical Methods

We analysed the data using the following steps:

- 1) The occurrence of oesophageal cancer cases among different relatives was described by the crude rate of oesophageal cancer for each familial relationship.
- 2) Cohort analysis of first degree relatives only and first degree relatives plus uncles and aunts was performed by comparing observed number of oesophageal cancer cases with expected numbers as obtained from local mortality rates. The period of risk was taken from birth until June 1992 or death. Computation of expected numbers was based on age-specific mortality rates of oesophageal cancer in Henan province from 1974 to 1976, corrected for regional differences, since only overall sex-specific rates were available for Huixian county. The correction factor used was calculated from the overall sex-specific oesophageal cancer mortality in Huixian county relative to that in Henan province. This

was 2.56 for males and 2.25 for females

$$\begin{aligned} (\lambda_{\text{age,males,Huixian}} &= 2.56 \lambda_{\text{age,males,Henan}}; \\ \lambda_{\text{age,females,Huixian}} &= 2.25 \lambda_{\text{age,females,Henan}}). \end{aligned}$$

Person-years at risk of death in family members was classified according to sex, 5-year age intervals and degree of relatedness to the oesophageal cancer proband. The mortality rates from 1974 to 1976 were applied to the whole time period considered since age-specific rates were available only from this time period (Henan Cancer Research Institute 1980). Oesophageal cancer mortality rates have been shown to have decreased by about 15% in 1983–1985 in the high incidence area.¹³ Standardized mortality ratios (SMR) were computed as the ratio between observed and expected numbers. Significance levels and 95% confidence intervals (CI) were calculated based on the Poisson distribution.

3) For further analysis of familial aggregation we used methods as described by Liang and Beaty.¹⁴ The index probands were excluded from the analysis, as proposed by Liang and Beaty¹⁴ and Tosteson *et al.*¹⁵ In a first step we calculated the frequency of oesophageal cancer cases among the families of varying size which allows testing the hypothesis of no familial aggregation using Tarone's one-sided score test.¹⁶ In a second step we estimate the odds ratios (OR) between family members which is independent of family size. The following notation applies: Let J be the number of families included in the analyses. For a single family of size n_j ($j = 1, \dots, J$) we denote with y_{ij} the binary outcome (0–1) of the i th individual in family j . The OR between the i -th and the k -th family member in the j -th family is:

$$OR_{ikj} = \frac{P(Y_{ij} = Y_{kj} = 0) \times P(Y_{ij} = Y_{kj} = 1)}{P(Y_{ij} = 0; Y_{kj} = 1) \times P(Y_{ij} = 1; Y_{kj} = 0)} \quad (i \neq k)$$

These OR can be estimated directly by calculating the number of concordant (n_{00} and n_{11}) and discordant pairs (n_{01}) within each family summed up for all families yielding a simple estimate.

$$OR_{ik} = n_{00} \times n_{11} / (n_{01}/2)^2$$

For further statistical modelling we estimate the log OR within an appropriate regression model. We use the logistic model,

$$\log \frac{P(Y_{ij} = 1)}{P(Y_{ij} = 0)} = \beta_0 + \beta' x_{ij1}$$

($i = 1, \dots, n_j$ $j = 1, \dots, J$) where x_{ij} is a vector of covariates of length p , and β is a vector of parameters of interest. In our analysis we used the covariates sex, age (in three

categories), and sex of the index case. As Y_{ij} and Y_{kj} are not independent, the correlation within families was described with OR regression models. We assume that the OR between family members is the same in all families ($OR_{ikj} \equiv OR_{ik}$) and that the log OR can be modelled as a function of only a few parameters, so that $\log OR_{ik} = H\gamma_z$. $H\gamma_z$ is a vector including OR for different relationships in the family. For example, we may assume $\gamma_z =$ constant (the same OR between any two members of the family). We also investigated more complex models, with γ_{ss} , γ_{sp} , and γ_{pp} assuming three different OR depending on whether the pairs are siblings (ss) parents (pp), or parent-sibling pairs (ps). It should be noted that the interpretation of regression parameters remains the same regardless of the family size.

The estimation of the parameters has been discussed in detail by Liang and Zeger,¹⁷ and Liang *et al.*¹⁸ We used GEE2 (a Pascal program with a GEE-procedure [generalized estimating equations]) provided by the authors.¹⁷ The program calculates estimates for the parameters and the standard errors. Parameter estimates and corresponding 95% CI are presented in the Tables.

RESULTS

The review of the registration books in the villages with regard to cancer incidence and mortality from 1987 to 1992 in Mengzhuang commune yielded crude mortality rates for oesophageal cancer of 127.9 per 100 000 for males and 72.3 per 100 000 for females and crude incidence rates of 142.1 per 100 000 and 79.9 per 100 000, respectively, confirming the high rates reported for Huixian county. A total of 279 incident cases occurred between 1987 and mid 1992. Family data were obtained from 251 index people (160 males and 91 females), comprising 90% of the 279 identified cases. The median participation rate of the villages was 93.3% with a range of 44.4–100%. Nonparticipants did not differ appreciably from participants with respect to sex and age at diagnosis. In seven instances where two cases occurred in the same family, the elder case was taken to be the index case. Therefore, data on 244 families from 155 male and 89 female index cases were used for the analysis. Two of the male index cases were diagnosed with cardia cancer.

A total of 6085 blood relatives (including 1887 third degree relatives) and 649 nonblood relatives were reported in the 244 families in addition to the index case. The mean family size was 28.9 per family. The reported number of first and second degree relatives with and without oesophageal cancer as well as the crude rates are shown in Table 1. The mean age at diagnosis was 61 years for index cases and the mean

TABLE 1 Occurrence of oesophageal cancer by family relationship

Relationship	Oesophageal cancer		Total no.	Crude rate %
	No	Yes		
Father	182	62	244	25.41
Mother	201	43	244	17.62
Grandfather	474	14	488	2.87
Grandmother	482	6	488	1.23
Brother	417	59	476	12.39
Sister	327	34	361	9.42
Son	466	4	470	0.85
Daughter	513	0	513	0.00
Uncle	478	63	541	11.65
Aunt	345	28	373	7.51

age at censoring was 55 years for sibs, 63 for fathers and 68 for mothers.

The reported crude rates of oesophageal cancer varied noticeably by relationship (Table 1). The lower rates reported for brothers and sisters compared to that for father and mother can be attributed to younger age of sibs (censored observation time). However, for uncles and aunts, underreporting must also be considered. Nevertheless, there was a consistent 1.5:1.0 male to female ratio in this study population which corresponds to that reflected by the SMR of oesophageal cancer in Huixian county (see METHODS). One can assume that reporting of oesophageal cancer occurrence among the parents is almost complete. The similar age distribution of the index cases by sex and that of the oesophageal cancer cases with known age at diagnosis among the parents and the sibs suggests that incomplete case reporting occurred at random (data not shown).

Compared to expected rates in Huixian county, the rate of oesophageal cancer among first degree relatives

of oesophageal cancer patients was 2.36-fold higher. SMR were 2.18 based on 117 observed and 53.68 expected cases among male relatives and 2.72 with 73 observed versus 26.81 expected among female relatives (Table 2). The corresponding risk ratios for both first and second degree relatives were 1.57 (172 observed, 109.68 expected) for males and 2.18 (96 observed, 43.99 expected) for females.

To identify some evidence of clustering within family, we first looked at the frequency of oesophageal cancer observed among the 242 families by varying family sizes. For this analysis we only considered deceased relatives in order to avoid censoring bias. Table 3 presents the distribution of families by different family sizes and numbers of cases of oesophageal cancer when only parents and siblings are considered. The numbers within parentheses are the expected number of families with the corresponding number of affected relatives under the null hypothesis of no familial aggregation which is a binomial distribution (given only for selected parts of Table 3). The larger numbers of families observed on the two tails of each row, especially evident for the family sizes of 2 and 3, suggest that there may be familial aggregation. Tarone's one-sided score test yielded a highly significant result ($P < 0.001$), giving support for the existence of within-family association. Comparable results were obtained when aunts and uncles were included in the calculations.

The OR between family members was estimated using parents and siblings. Among 1112 possible pairs of relatives, there were 92 where both relatives were affected, 648 where neither were affected, and 372 which were discordant. This gave a point estimate of 1.82 and a 95% CI of 1.24–2.66, again providing evidence for familial aggregation (Table 4). Breaking down the family into classes of relatives, the crude OR were 2.37

TABLE 2 Observed and expected oesophageal cases, person-years and standardized mortality ratio (SMR) of oesophageal cancer among relatives of oesophageal cancer patients in China

Relationship	Observed	Expected	Person-years	SMR	95% CI
First degree:					
Male	117	53.68	25 532	2.18	(1.81–2.62)
Female	73	26.81	21 549	2.72	(2.14–3.45)
Second degree ^a :					
Male	55	56.00	19 182	0.98	(0.74–1.28)
Female	23	17.18	11 660	1.34	(0.85–2.01)
First and second degree ^b :					
Male	172	109.68	44 714	1.57	(1.35–1.83)
Female	96	43.99	33 209	2.18	(1.77–2.66)

^a Includes uncle and aunt.

^b Includes father, mother, brother, sister, uncle, aunt.

TABLE 3 Frequency of oesophageal cancer by family size (deceased relatives)

First degree relatives (parents + siblings)							
Family size	No. affected ^a						Total
	0	1	2	3	4	6	
1	11	12	0	0	0	0	23
2	50 (46.6)	19 (25.8)	7 (3.6)	0	0	0	76
3	37 (32.1)	17 (27.4)	14 (7.8)	0 (0.7)	0	0	68
4	11 (8.9)	10 (13.4)	9 (7.6)	1 (1.9)	1 (0.2)	0	32
5	8 (6.4)	8 (9.7)	5 (5.8)	2 (1.8)	1 (0.3)	0 (0.02)	24
6	1 (1.2)	4 (3.0)	3 (3.2)	0 (1.8)	2 (0.6)	0 (0.2)	10
7	0 (0.2)	1 (0.8)	3 (1.4)	0 (1.4)	0 (0.8)	1 (0.06)	5
8	0	0	1	0	0	0	1
9	1	0	1	0	0	0	2
10	0	0	1	0	0	0	1
	119	71	44	3	4	1	242 ^b

^a Expected number of families in brackets.

^b The difference in the total number of families is due to two families where there were no deceased first-degree relatives.

for parent–parent, 2.01 for parent–sib and 1.16 for sib–sib pairs. Adjustment for covariables such as sex, age and sex of index case led to some decrease in the magnitude of OR but the overall reduction was not substantial. Adjustment for family size did not alter the risk estimates. The results suggest that the pairwise association was weak between sibs. The associations between parents and between parents and offspring were equally strong.

DISCUSSION

The increased rate of oesophageal cancer observed among relatives of oesophageal cancer patients in a

high incidence area in China confirms the existence of familial aggregation of cancer in this population. The excess risk was apparent for first degree relatives where the magnitude of increase was of the order of two to three. We believe that this estimate is not strongly biased although the calculation of expected numbers of oesophageal cancer among relatives was based solely on mortality rates from 1974–1976. Mortality rates for oesophageal cancer in this region were shown to have decreased in 1983–1985. If the mortality rates have also decreased from the decade before 1974–1976, we would have overestimated deaths due to oesophageal cancer after 1974–1976 and underestimated such deaths in the prior decades. Since the occurrence of oesophageal cancer among the relatives were equally distributed in the decades before and after 1974–1976, the deviance from the true expected numbers in either direction may be balanced. Otherwise, if the rates have remained fairly constant until 1974–1976, we would have achieved a conservative estimate of the SMR. A two- to threefold increased risk associated with family history has been previously reported for oesophageal cancer and also for other cancer sites.^{6,7,9,19,20} The reduction in excess relative risk in second degree relatives is consistent with that expected for each degree of relationship in case of a simple genetic model.²¹ However, this may have been influenced by recall bias since the knowledge of disease occurrence among relatives tend to reduce by degree of relationship. This was reflected by the crude rates of oesophageal cancer we obtained for the different classes of relatives.

Further evidence for clustering within families was provided by the observation of excessive numbers of families with either no further occurrence of oesophageal cancer in addition to the index case or multiple cases using Tarone’s one-sided score test for binomial distributions. This was particularly evident for family sizes

TABLE 4 Results of odds ratio regression models, number of pairs by affection status and crude OR estimate

Pairs of relatives	Affective status in pairs			OR	Model			
	Both	None	Discordant		No covariables		Adjusted for sex, age, sex of index case	
	n_{11}	n_{00}	n_{01}	$\frac{n_{00} n_{11}}{\left(\frac{n_{01}}{2}\right)^2}$	OR	95% CI	OR	95% CI
All pairs combined	92	648	372	1.72	1.82	(1.24–2.66)	1.73	(1.16–2.57)
Parent–parent	16	131	60	2.33	2.37	(1.20–4.66)	2.33	(1.13–4.82)
Sib–sib	23	173	117	1.16	1.16	(0.63–2.08)	1.09	(0.59–2.03)
Sib–parent	53	344	195	1.92	2.01	(1.30–3.10)	1.88	(1.18–2.97)

of 2 and 3 where the number of families was reasonably large and a range of numbers of affected individuals was available for differentiation. Although the results support the existence of within-family association, this analysis fails to account for variance due to between-pairs correlation and to family and/or individual specific variables such as age. Therefore a series of models was fitted by applying the GEE method. The covariables sex, age and sex of index case, however, did not have a profound impact on the estimation of familial aggregation. The pairwise OR obtained suggest that the risk of a family member is increased when his/her relative is affected rather than unaffected reflecting familial aggregation. The risk estimate is in line with that provided by the SMR and supports the hypothesis that familial aggregation exists, associated with an increased risk of oesophageal cancer for first degree relatives.

Further analyses breaking down the family into classes of relatives were performed in an attempt to anticipate more sophisticated genetic studies. There was a clear association between parent and sib but none between sibs. With an autosomal recessive Mendelian inheritance, as suggested by Carter,¹⁰ we would have expected to observe a stronger association between sibs. A possible explanation for this lack of association could be the censored data of the sibs compared to the parents. Due to the lower mean age at censoring, sibs have a lower probability of having developed oesophageal cancer, thus the analysis yields a less precise estimate. Also, a lower risk in parents than siblings might indicate recessive inheritance. We did not find a higher SMR for brothers and sisters compared to parents. The decrease in mortality from oesophageal cancer in the past decade will have had a greater impact on the occurrence of oesophageal cancer among sibs than in parents. Thus the SMR for sibs would be more conservative than that for the parents. Another possible explanation is a birth cohort effect. However, the size of this data set did not allow further differentiation by birth cohort after age was adjusted for. As age had only a minor effect on the correlation structure, further adjustment by birth cohort is unlikely to modify the estimates.

The pairwise association between parents suggest a strong involvement of environmental factors which are known to exist for oesophageal cancer in China.^{3,6} If strong environmental factors were operating in this study population, an association between sibs should also have been found. The absence of such an observation suggests that environmental factors may have a stronger action after childhood. Although it is interesting to speculate on the possible involvement of genetic and environmental factors which appear to be indicated

by these findings, the methods employed are only suitable for assessing familial aggregation in general. The familial aggregation as quantified is moderate and could be partly explained by environmental factors. Nevertheless, there may still be genetic predisposition for the disease in a small proportion of the population. More studies should provide further understanding of the contribution of genetic and environmental determinants in the aetiology of oesophageal cancer.

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