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Segregation Analysis of Esophageal Cancer in 221 High-Risk Chinese Families

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Background: Until recently, environmental factors were considered of greatest importance in the etiology of esophageal cancer. Recent studies, however, have suggested that genetic factors also have a role. **Purpose:** Since no formal genetic study of this cancer has been previously reported, we carried out a statistical analysis to determine how important genetic factors are in the etiology of esophageal cancer in high-incidence areas of North China. **Methods:** Using a logistic regressive model, we performed a segregation analysis on 221 high-risk nuclear families from the Yaocun Commune, Linxian, Henan Province of China, with at least one affected family member and with all offspring aged 40 years or older. Three models, the mendelian, the environmental, and the no-transmission models, were each compared with the general-transmission model that incorporated both genetic and environmental factors. **Results:** According to Akaike's Information Criterion, the mendelian model provided the best fit for the data. By the chi-square test, the mendelian inheritance model was not rejected, but the environmental and the no-transmission models were both rejected. **Conclusion:** The segregation analysis indicated an autosomal recessive mendelian inheritance, with the alleged mendelian gene present at a fre-

quency of 19%, causing 4% of this population to be predisposed to develop esophageal cancer. Large, unmeasured, residual familial factors, however, were also significant. **Implications:** Both an autosomal recessive gene and unexplained environmental factors appear to be important in the etiology of esophageal cancer in the subpopulation studied. [*J Natl Cancer Inst* 84:771-776, 1992]

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There is a large international variation in esophageal cancer mortality rates. In South Africa, Central Asia, Iran, India, and North China, carcinoma of the esophagus is one of the leading causes of cancer death (1-4). In North China, the reported esophageal cancer mortality rates are the highest in the world. Interestingly, mortality rates in this area vary dramatically among contiguous and nearby counties. Li (5) reported a 651-fold difference for males and a 670-fold difference for females in the mortality rates between counties with the highest rates (254.77 per 100,000 males and 161.11 per 100,000 females) and counties with the lowest rates (0.39 per 100,000 males and 0.24 per 100,000 females).

One particular county, Linxian, in the Henan Province of North China has received worldwide attention over the past decade for rates 100 times those found in neighboring counties (6). In 1959, epidemiologic studies began in Linxian, and a cancer registry was started. For the next 25 years, these studies showed that esophageal cancer eventually claimed the lives of approximately one of every four males and one of every six females and accounted for one quarter of all deaths in the county each year (7).

Over the past two decades, many studies have been conducted on the etiologic and epidemiologic factors associated with esophageal cancer in China (5,8,9). Environmental factors that have been implicated as causally related include consumption of moldy foodstuffs, pickled vegetables, and steaming hot gruel; consumption of high levels of nitrosamines or various trace elements; nutritional deficiencies; the occurrence of fungal infections; and poor personal and oral hygiene.

Epidemiologic surveys have also disclosed a strong familial aggregation in the occurrence of this tumor (8,10,11). High-incidence families were studied in two communes in Linxian in 1971 (9) and in 1974 (11). These studies revealed striking similarities in the esophageal cancer death rates for blood relatives and significantly lower esophageal cancer death rates for non-blood relatives living in the same household. Ding and Wu (11) concluded that "there seems to be unequivocal evidence of genetically determined susceptibility to esophageal cancer." The purpose of our study was to investigate the importance of the genetic component that appeared to be contributing to the risk of esophageal cancer in these families. This study was conducted as a collaboration among scientists at the Cancer Institute of the Chinese Academy of Medical Sciences, Beijing, the National Cancer Institute, Bethesda, Md., and the Howard University Cancer Center, Washington, D.C.

Patients and Methods

For the segregation analysis, we selected 221 high-risk nuclear families, consisting of a father, a mother, and their offspring, from the Yaocun Commune, Linxian, China. In each family selected, at least one person was affected with esophageal cancer and all the offspring were aged 40 years or older. The nuclear families were selected from pedigrees first studied more than 10 years ago in Linxian (10).

In the late 1970s, data were collected from the Yaocun Commune, Linxian, Henan Province, by trained doctors using a structured questionnaire. From the total population of the commune, all existing patients with either cytologically confirmed esophageal cancer or carcinoma of the gastric cardia were identified. The history of esophageal cancer was then traced among

the relatives of these patients (i.e., probands) in four successive generations—including parents, grandparents, siblings, offspring, and all other relatives of both the siblings and the offspring living in the commune. By the end of 1980, esophageal cancer (including carcinoma of the gastric cardia) was reported in 180 living patients. All diagnoses were confirmed by Yaocun Commune Hospital either by x ray and/or by cytology.

Information concerning the vital status of all members of the pedigrees of these patients was collected in 1989. Extension of the pedigrees was minimal, did not utilize a specific sampling rule, and was performed mainly to fill in information gaps. Deaths after 1959 (the date the Linxian Cancer Registry was opened) were confirmed by the registry. However, 29% of the esophageal cancer deaths occurred before the registry was opened, and these were reported and checked by recall (memory) only.

Of the updated pedigrees, 24 had four or more esophageal cancer patients; these were called high-risk families. Upon inspection of these 24 high-risk pedigrees, we found that, for a high percentage of them, data were missing on age (unaffected persons) or on age at onset of cancer (affected persons). Age at onset of disease is a particularly important data item to collect, since persons unaffected at the time of examination could present with the disease at an older age. We therefore searched the sample for a subset in which the effect of varying age at onset of disease could be ignored in the analysis. We found that, among 221 high-risk nuclear families satisfying our other criteria, the distribution (i.e., the mean and the variance) of the ages at the onset of cancer in persons affected with esophageal cancer was similar to the age distribution of unaffected persons. Thus, we were convinced that the effect of varying age at onset of disease was negligible in that subset of families. If the ages of affected persons at onset of disease had been greater than the ages of unaffected persons, one could presume that the unaffected persons had yet to reach an age at which the onset of esophageal cancer might occur (i.e., unaffected persons might be incorrectly classified as disease free, since they might acquire the disease at a later time).

Thus, the sampling frame used for the data analyzed in this study was the population of 221 nuclear families in the Yaocun Commune, Linxian, China, in which at least one person has esophageal cancer and all offspring are aged 40 years or older. This sampling frame is not perfect; 1.8% of the persons in the sample whose ages were recorded were below 40 years of age. These persons consisted of parents who died before the age of 40 years. Although all of the offspring were aged 40 years and older, the unaffected persons in our sample are probably still censored in the sense that they could become affected in their later years. The percentage (40%) of the affected persons in the sample is unusually high, however, and the age distribution of affected persons was almost identical to that of unaffected persons (Table 1). Hence, censoring is not likely to be important.

Statistical Methods

Segregation analysis was performed on the disease trait expressed as a dichotomy (i.e., affected or unaffected with esophageal cancer), using the logistic regressive model described by Bonney (12). As noted in the introduction, genetic and environmental factors have been implicated in the

Table 1. Mean age of selected nuclear family members by gender and by disease status

	Mean age, y	SD	No.*
Gender			
Males	58.67	11.05	384
Females	59.62	11.79	321
Disease status			
Affected	59.79	9.94	279
Unaffected	58.66	12.24	426

*Cases for which age information is known.

etiology of esophageal cancer. Because family members tend to share not only genes, but also environmental exposures and lifestyles, focusing on only one of these factors in the analysis of family data may lead to results confounded by other factors. The regressive model provides a statistical method for analyzing the effects of important genetic and environmental risk factors (either unmeasured or measured). The regressive model accounts for familial correlations by specifying a regression relationship between a person's phenotype and a set of explanatory variables, including his or her genotype with respect to specific loci, the phenotypes of older relatives, and environmental and lifestyle covariates.

This method is appealing because it simultaneously provides for the effects resulting from important genes and those resulting from complex patterns of residual familial correlations (including sib-sib, spouse-spouse, and parent-offspring phenotypic) without postulating explicit genetic or environmental causal mechanisms. Of course, known causal mechanisms can be incorporated by choosing suitable parametrization. The mixed model (13) and the unified model (14) are equivalent to special cases of the class D regressive model (15-17). The version of the regressive model used in this article allows investigators to test for asymmetric familial effects to determine, for instance, whether the risk of having esophageal cancer when the father is affected is the same as the risk when the mother is affected. In contrast, the mixed and unified models do not allow for such testing. Another feature of the regressive model, which has not yet been developed for the mixed and unified models, is the direct incorporation of covariate effects (as is standard in epidemiology). One example is the effect of gender in this article. Information on other covariates such as alcohol consumption and cigarette smoking was missing in our recorded data for a large number of persons; therefore, these covariates were not considered in our analysis. In the regressive model (and also in the mixed and unified models), the effects of unmeasured covariates were subsumed either in the residual familial correlations or in the regressions. The variables were coded as follows:

- Y = 1 for affected, 0 for unaffected;
- Z_{F1} = 1 for father affected, 0 for otherwise (unaffected or missing);
- Z_{F2} = 1 for father unaffected, 0 for otherwise (affected or missing)

[Thus, three possible values are allowed for a person's father's phenotype:

- $Z_{F1} = 1, Z_{F2} = 0$ for father affected,
- $Z_{F1} = 0, Z_{F2} = 0$ for father unobserved,
- $Z_{F1} = 0, Z_{F2} = 1$ for father unaffected.]

- Z_{M1} = 1 for mother affected, 0 for otherwise (unaffected or missing);
- Z_{M2} = 1 for mother unaffected, 0 for otherwise (affected or missing);
- Z_{S1} = 1 for spouse affected, 0 for otherwise (unaffected or missing);
- Z_{S2} = 1 for spouse unaffected, 0 for otherwise (affected or missing);
- Z_{OS1} = number of affected older sibs;
- Z_{OS2} = number of unaffected older sibs;
- X = 1 for males, 0 for females.

For any person, let Θ be the logarithm of the odds (logit) of having esophageal cancer, i.e.,

$$\Theta = \log[Pr(Y = 1)/Pr(Y = 0)].$$

Then our regressive logistic model, the class D regressive model of Bonney (12), expresses the logit of the disease as a function of the genotype g , the phenotypes (disease status) of the spouse, the father, the mother, the older sibs, and other covariates. Thus, the logit (the logarithm of the odds of having esophageal cancer) is as follows:

$$\Theta = \alpha(g) + \gamma_{S1}Z_{S1} + \gamma_{S2}Z_{S2} + \gamma_{F1}Z_{F1} + \gamma_{F2}Z_{F2} + \gamma_{M1}Z_{M1} + \gamma_{M2}Z_{M2} + \gamma_{OS1}Z_{OS1} + \gamma_{OS2}Z_{OS2} + \beta X.$$

The β 's, γ 's, and α 's are unknown parameters, with the following interpretation on the logit scale: β is the regression coefficient for gender (X); since X is coded 1 for males and 0 for females, the females have the baseline value, and β is the increase (or decrease if negative) in the logarithm of the odds of a male being affected. The γ 's are the regression coefficients for familial variables; thus γ_{M1} is the increase (or decrease if negative) in the logit if the mother is affected, γ_{M2} is the change in the logit if the mother is unaffected, and a person's logit is unchanged if the esophageal cancer status of the mother is unknown. The other γ 's are similarly defined. This parametrization 1) allows for the possibility that familial effects are asymmetric on the logit scale and 2) has been shown to include the classical parametrization of the polygenic inheritance, if that is the true state of nature (18) for a discussion of coding schemes (17). The α is a person's baseline risk (on the logit scale) and may depend on genotype g .

For segregation analysis, mendelian inheritance, if present, was presumed to be through a single autosomal locus with two alleles, A and B . Allele A was associated with the affected state, having a frequency of occurrence in the population of q_A . The three possible genotypes, labeled AA , AB , and BB , were assumed to be at Hardy-Weinberg equilibrium. As noted above, the baseline risk, α , can depend on genotype, so for the three genotypes, we have α_{AA} , α_{AB} , and α_{BB} . If the gene A is recessive, $\alpha_{AB} = \alpha_{BB}$; if it is dominant, $\alpha_{AA} = \alpha_{AB}$; and if it is codominant, α_{AA} , α_{AB} , and α_{BB} are not restricted.

The quantities describing parent-offspring transmission of the mendelian factor A are τ_{AAA} , τ_{ABA} , and τ_{BBA} (19,20) and denote the probability of transmitting the allele A for a parent of genotypes AA , AB , and BB , respectively. Mendelian transmission then corresponds to the case in which $\tau_{AAA} = 1$, $\tau_{ABA} = 1/2$, and $\tau_{BBA} = 0$. Familial transmission of other factors that are not directly observable, however, can also be described with the τ 's, except that there will be no reason to assume that τ will take the values 1, $1/2$, and 0. Thus, the τ 's are generally

allowed to range from 0 to 1, and the term ousiotype (21) has been proposed to describe any factor (genetic or other, e.g., viral or behavioral) transmitted from parent to offspring. A genotype is a particular case of an ousiotype that corresponds to mendelian transmission.

The four models used in our analysis were defined as follows: 1) In the "no-transmission" model, no detectable ousiotype was present in the population (i.e., the baseline risk α is independent of ousiotype, if any exists). 2) In the "environmental" or " τ 's equal" model, the values of τ are equal, i.e., $\tau_{AAA} = \tau_{ABA} = \tau_{BBA}$. 3) In the "mendelian-transmission" model, τ assumes the following specific values: $\tau_{AAA} = 1$, $\tau_{ABA} = 1/2$, and $\tau_{BBA} = 0.4$. In the "general-transmission" model, all of these components (whether genetic, environmental, or other) were included (i.e., the τ 's were unrestricted).

"Residual transmission" occurs when the regression coefficients of the familial variables (the γ 's) are nonzero. In this case, factors other than those specified by the model contribute to the familial transmission of the disease.

It is assumed that transmission from the parents occurs independently, corresponding to random mating. Different modes of transmission were hypothesized, including mendelian inheritance of a single recessive allele *A*, mendelian inheritance of a single dominant allele *A*, mendelian inheritance of single susceptibility allele *A* with no dominance restriction (the codominant model), the no-transmission model, and the general-transmission model.

To test which of the different hypotheses of transmission was the most probable, we compared each of three models (the mendelian, the environmental [τ 's equal], and the no-transmission models) with the fourth model (the general-transmission model). The models were fitted by maximum likelihood methods. Complete (truncate) ascertainment correction was applied because, with reference to our sampling frame, every affected person was a proband. Complete ascertainment implies that the families were randomly selected from a population of nuclear families in which there was at least one affected person and in which the offspring were aged 40 years or older.

The Akaike's Information Criterion (AIC) (22), defined as $AIC = -2 \ln L + [2 \times (\text{number of parameters estimated})]$, was used to decide the model that provided the best fit for the data; the model with the minimum AIC fit the data best. The AIC does not show, however, that the best-fitting model fits significantly better than another model; therefore, likelihood (*L*) ratio tests were performed for that purpose. The likelihood ratio test is a chi-squared test defined, using the mendelian model as an example, as $\chi^2 = [(-2 \ln L_{\text{mendelian}}) - (-2 \ln L_{\text{general transmission}})]$, with the degrees of freedom (df) given by $df = \text{the difference in the number of estimated parameters for the two hypotheses}$.

Finally, we examined the symmetry of familial effects. We simultaneously tested whether $\gamma_{F1} = \gamma_{M1}$ and $\gamma_{F2} = \gamma_{M2}$, to determine if the increased risk associated with having an affected father was equivalent to that associated with having an affected mother and if the reduced risk associated with having an unaffected father was equivalent to that associated with having an unaffected mother. We also tested simultaneously whether $\gamma_{F1} = -\gamma_{F2}$ and $\gamma_{M1} = -\gamma_{M2}$, to determine if the

magnitude of the increase in risk associated with having an affected father was equal to the magnitude of the reduction in risk associated with having an unaffected father and whether the magnitude of the increase in risk associated with having an affected mother was equal to the magnitude of the reduction in risk associated with having an unaffected mother.

Results

Main Features of the Data

Table 1 presents the age distribution in the 221 nuclear families selected (a total of 705 persons): 13 (1.8%) persons were below age 40 years; these were persons who died before age 40 years but had children who lived 40 years or longer and were therefore included in our data. The age distributions of males and females were not statistically different ($P = .2743$); the mean ages were 58.67 (SD = 11.05) for males and 59.62 (SD = 11.79) for females. The age distributions were also similar for persons affected with esophageal cancer and for unaffected persons; the mean ages were 59.79 (SD = 9.94) for affected persons and 58.66 (SD = 12.24) for unaffected persons; they were not statistically different ($P = .1965$).

Segregation Analysis Results

The results of comparing each of the three models described above with the general-transmission model are shown in Table 2. Each model presented assumes a recessive mode; i.e., $\alpha_{AB} = \alpha_{BB}$. By the criteria of determining the minimum AIC, the mendelian hypothesis was the best fitting of the four compared models. By the chi-square test, the mendelian transmission model was not rejected ($P = .489$), while the environmental (τ 's equal) model ($P < .0001$) and the no-transmission model ($P < .001$) were rejected when each was compared with the general-transmission model. The mendelian model was also fitted assuming dominant and codominant modes of transmission; the parameter estimates of the codominant mode were compatible with those for the recessive mode of transmission. It therefore appears that a recessive major gene is segregating in the Yaocun Commune families.

In Table 3, more parsimonious versions of the autosomal recessive mendelian model were compared. We were interested in knowing whether the alleged major gene by itself sufficiently accounted for the familial aggregation of esophageal cancer. Note that the model without the gender covariate was similar to the recessive mendelian model that included gender as a covariate ($P > .10$). Therefore, gender did not appear to be an important covariate in these data if we accounted for other elements of family history. Both the autosomal recessive mendelian model with no residual correlations ($P < .01$) and the model with no sibling correlations but with spousal and parental-offspring correlations ($P < .02$) were rejected against the mendelian model with residual correlations. Thus, residual effects did appear to have an important role in disease transmission, and all three components of the residual effect (parent-offspring, spouse-spouse, and sib-sib) appeared to be significant.

Our results indicated an asymmetry of familial effects in these data. The simultaneous test of $\gamma_{F1} = \gamma_{M1}$ and $\gamma_{F2} = \gamma_{M2}$ yielded a χ^2 of 8.2464 with 3 df and $P = .041$. The test of

Table 2. Parameter estimates from segregation analysis of esophageal cancer

Parameter	Model			
	Mendelian	Environmental	No transmission	General transmission
T_{AAA}	1.0*	0.0537	---	1.0
T_{ABA}	0.5*	0.0537	---	0.4237
T_{BBA}	0.0*	0.0537	---	0.0483
q_A	0.1874	0.1236	1.0*	0.1890
α_{AA}	14.1725	48.0375	-2.1834	24.9055
α_{AB}	-1.4317	-2.3068	-2.1834	-0.5924
α_{BB}	-1.4317	-2.3068	-2.1834	-0.5924
γ_{S1}	-1.1758	0.0851	0.0939	-2.5222
γ_{S2}	-0.4750	0.6248	0.5949	-1.2968
γ_{F1}	0.2224	-0.0251	-0.1153	-0.1326
γ_{F2}	-0.3311	0.3735	0.2761	-4.0177
γ_{M1}	-2.3570	-0.6543	-0.6457	-5.4057
γ_{M2}	-0.9476	0.3512	0.3385	-1.4788
γ_{OS1}	0.0470	-0.2930	-0.2779	-0.4839
γ_{OS2}	-6.3329	0.6438	0.6337	-9.2752
β_1	-0.9076	0.2434	0.2376	-2.2224
$-2 \ln L$	653.3832	667.6638	667.6627	651.9514
AIC	679.3832	695.6638	691.6627	683.9514
χ^2	1.4318	15.7124	15.7113	---
df†	2	1	3	---
P	.489	.000	.001	---

*The parameters were fixed to the values marked with the star.

†Conservative df.

Table 3. Residual correlations and gender covariate influences

Parameter	No gender covariate	No residual correlation	No sibling correlation	Mendelian model
T_{AAA}	1.0	1.0	1.0	1.0
T_{ABA}	0.5	0.5	0.5	0.5
T_{BBA}	0.0	0.0	0.0	0.0
q_A	0.1982	0.2394	0.2911	0.1874
α_{AA}	13.9755	0.7415	1.3253	14.1725
α_{AB}	-2.1425	-2.3407	-3.0360	-1.4317
α_{BB}	-2.1425	-2.3407	-3.0360	-1.4317
γ_{S1}	-0.2592	---	0.3003	-1.1758
γ_{S2}	0.1992	---	0.8265	-0.4750
γ_{F1}	0.4648	---	-0.5062	0.2224
γ_{F2}	-0.2455	---	-1.0602	-0.3311
γ_{M1}	-2.0314	---	-0.9267	-2.3570
γ_{M2}	-1.0024	---	-0.4311	-0.9476
γ_{OS1}	0.0783	---	---	0.0470
γ_{OS2}	-6.6143	---	---	-6.3329
β_1	---	---	---	-0.9076
$-2 \ln L$	656.0067	691.2145	664.5402	653.3832
AIC	680.0067	699.2145	684.5402	679.3832
χ^2	2.6235	37.8313	11.157	---
df	1	9	3	---
P	.105	.000	.011	---

$\gamma_{F1} = -\gamma_{F2}$ and $\gamma_{M1} = -\gamma_{M2}$ yielded a *P* value of .050. These results indicate that no residual maternal effect existed, but there were significant residual paternal and sibling effects. We interpret this result to mean that familial transmission of esophageal cancer from the paternal line is stronger than that from the maternal line in these families.

Discussion

The segregation analysis of 221 high-risk nuclear families from the Yaocun Commune, Linxian, China, reveals the effects of an alleged mendelian recessive gene that is present (at a frequency of 19%) in the population we studied and of unexplained residual familial factors. Thus, the proportion of persons who are predisposed to develop esophageal cancer as a

result of this recessive gene is the square of this frequency, or 4% of the population studied.

The results of our segregation analysis support the view that there is a genetically determined susceptibility to esophageal cancer. These results are the first reported evidence implicating a major gene in the etiology of esophageal cancer. Because of our role for the selection of esophageal, we stress that the inference here of a mendelian factor applies only to the sub-population we studied, i.e., to nuclear families in the Yaocun Commune, Linxian, China, in which at least one person is affected with esophageal cancer and all offspring are aged 40 years or older.

Epidemiologic studies of esophageal cancer in China have implicated environmental factors in the etiology of esophageal cancer. These factors include consumption of moldy food-

stuffs, pickled vegetables, and steaming hot gruel; consumption of high levels of nitrosamines or various trace elements; nutritional deficiencies; the occurrence of fungal infections; and poor personal and oral hygiene. These factors were not taken into account in this study. Exposure to some environmental risk factors may well be related to being a member of a certain family, but there is no reason to believe that the disease pattern resulting from these shared environmental exposures among relatives should mimic that resulting from mendelian inheritance. Moreover, the regressive models used for this analysis allowed for unmeasured effects (environmental or otherwise) in the residual familial parameters.

Segregation analysis is not foolproof, and environmental factors can masquerade as mendelian factors. It has been shown, however, that if the environmental (τ 's equal) hypothesis is rejected against the general-transmission model while the mendelian hypothesis is accepted, as in the present study, false inference due to masquerading environmental factors is minimized (23).

As in all studies of this type, the finding of mendelian inheritance is preliminary until the gene is found. This search will take time. The alleged gene by itself does not account for all cases; unexplained factors, particularly environmental ones, are probably important. The greatest challenge will be to carefully delineate the relative contribution of genetic and environmental factors to the etiology of esophageal cancer.

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- Letter of invitation from the prospective host.
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- Statement concerning the provision of 50 percent of financial support by European sources. Non-EORTC member country candidates must continue at full salary at the home institution for the duration of the exchangeship.
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