

Squamous Esophageal Histology and Subsequent Risk of Squamous Cell Carcinoma of the Esophagus

A Prospective Follow-Up Study from Linxian, China

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Background. Linxian, China, has some of the highest rates of esophageal cancer in the world. Previous authors have proposed that esophagitis, atrophy, and dysplasia may be precursor lesions of esophageal cancer in such high risk populations.

Methods. To examine the relationship between squamous esophageal histology and subsequent esophageal cancer in Linxian, the authors prospectively followed 682 participants of a 1987 endoscopic survey for 3.5 years and compared their initial biopsy diagnoses with the occurrence of squamous cell carcinoma during this follow-up period.

Results. Squamous cell carcinoma of the esophagus was identified in 52 (7.6%) of the participants during the follow-up period. After adjusting for potential confounding factors, relative risks (95% confidence intervals) for squamous cell carcinoma incidence by initial histologic diagnoses were as follows: normal, 1.0 (reference); basal

cell hyperplasia, 2.1 (0.4–9.8); mild dysplasia, 2.2 (0.7–7.5); moderate dysplasia, 15.8 (5.9–42.2); severe dysplasia, 72.6 (29.8–176.9); dysplasia not otherwise specified, 22.9 (6.7–78.0); and carcinoma in situ, 62.5 (24.1–161.9).

Conclusion. In this study, moderate dysplasia, severe dysplasia, and carcinoma in situ were the only histologic lesions associated with a significantly increased risk of developing squamous cell carcinoma of the esophagus within 3.5 years after endoscopy. Increasing grades of dysplasia were associated with increasing risk, but severe dysplasia and carcinoma in situ had similar degrees of risk, findings that suggest a continuous spectrum of esophageal intraepithelial neoplasia, without morphologically distinguishable dysplasia and in situ carcinoma. A longer follow-up will be necessary to fully evaluate the less severe diagnostic categories, which may take more than 3.5 years to affect the occurrence of squamous cell carcinoma in this high risk population. *Cancer* 1994; 74: 1686–92.

Key words: esophagus, esophageal neoplasms, precancerous conditions, endoscopy, pathology, squamous dysplasia, squamous cell carcinoma, follow-up studies.

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Linxian, China, has some of the highest rates of esophageal cancer in the world.¹ During 1959–1981, the annual age-adjusted mortality rates for esophageal cancer among 40–69-year-olds were 470 per 100,000 for all of Linxian county and 760 per 100,000 for residents in Linxian's northern communes, rates that were 100–150 times comparably adjusted rates for U.S. whites.² Since 1983, the Cancer Institute of the Chinese Academy of Medical Sciences and the U.S. National Cancer Institute have collaborated to perform two nutrition intervention trials among 40–69-year-olds in four northern communes of Linxian to test the hypothesis that nutritional

supplementation can affect the incidence and mortality of esophageal cancer in this population.²⁻⁵ As a part of this collaboration, an endoscopic survey was performed in 1987 among Dysplasia Trial participants.^{3,6,7} The current paper reports a 3.5-year follow-up study of the 682 subjects in that survey who had one or more satisfactory esophageal biopsies and were free of cancer at the beginning of the follow-up period. The purpose of this analysis was to correlate the initial squamous histologic findings with subsequent development of squamous cell carcinoma of the esophagus.

Materials and Methods

Endoscopic Survey

The endoscopic examination was conducted among subjects enrolled in the Dysplasia Trial in Linxian, a 6-year double-blind prospective nutrition intervention trial limited to persons with a previous cytologic diagnosis of esophageal dysplasia.^{3,4} Active intervention, consisting of daily tablets containing 26 vitamins and minerals at two to three times U.S. recommended daily allowances or matched placebos began on May 1, 1985, and ended on April 30, 1991.^{3,4}

In November and December 1987, after 30 months of active intervention, 833 Dysplasia Trial subjects underwent endoscopy. The study was approved by the Human Research Review Committee of the Cancer Institute of the Chinese Academy of Medical Sciences, and informed consent was obtained from each subject before the procedure. Details of subject selection, refusal rates, and participant characteristics have been described previously.⁷

During endoscopy, the entire esophagus and stomach were visually examined, and one or more 2.8-mm biopsy specimens were taken from all focal lesions. If no focal lesions were found, a standard site in the mid-esophagus was sampled. The biopsy specimens were fixed in 10% buffered formalin or 95% ethanol, embedded in paraffin, cut in 5- μ m sections, and stained with hematoxylin and eosin.

Histologic Categories

The biopsy slides were read jointly by three pathologists (S.M.D., K.J.L., L.F.S.), without knowledge of the patient's history or treatment group or the visual endoscopic findings. The histologic criteria were based on previous descriptions.^{6,8-10}

Normal. A stratified squamous epithelium was present that showed no features diagnostic of the other histologic categories listed below. Mature squamous cells with abundant clear cytoplasm, scattered lympho-

cytes, and compressed nuclear fragments ("squiggle cells") were occasionally seen in the epithelium. The lamina propria, if present, commonly contained a few scattered mononuclear inflammatory cells.

Basal cell hyperplasia. An otherwise normal epithelium had a basal zone thickness greater than 15% of total epithelial thickness, without elongation of lamina propria papillae or other abnormality.

Acanthosis. An otherwise normal epithelium was greater than or equal to 0.5-mm thick.

Esophagitis. One or more of the following three criteria were present: elongation of lamina propria papillae into the upper third of the epithelium together with basal cell hyperplasia greater than 15% of total epithelial thickness; epithelial infiltration by neutrophils or eosinophils; or a dense nonfollicular infiltrate of mononuclear inflammatory cells or neutrophils in the lamina propria.

Squamous dysplasia. Nuclear atypia (enlargement, pleomorphism, and hyperchromasia), loss of normal cell polarity, and abnormal tissue maturation were present in the lower third (mild), in the lower two thirds (moderate), or in all thirds (severe) of the epithelium, without full-thickness involvement or invasion. Biopsy specimens containing dysplastic cells that could not be graded because of biopsy size or orientation were categorized as squamous dysplasia, not otherwise specified.

Carcinoma in situ. Dysplastic squamous cells were present throughout the full thickness of the epithelium, without invasion.

Squamous cell carcinoma. Neoplastic squamous cells were present that had invaded through the basement membrane.

Follow-Up Procedures

Incident cancers and deaths were identified through several methods that assured essentially complete ascertainment of these events.³ All medical facilities, including commune hospitals, the Linxian County Cancer Hospital, and the cancer hospital in the prefecture capital of Anyang notified investigators of all cancer diagnoses among residents of the communes in the Dysplasia Trial. Participants with cancer symptoms and those who died of any cause were identified by village doctors on their monthly visits to deliver the intervention pills. Additional visits to look for symptomatic persons were made by a medical team from the Cancer Institute of the Chinese Academy of Medical Sciences in Beijing based at a field station in Yaocun commune. Symptomatic persons were referred to the medical team field station or their commune hospital for further evaluation. Case records and diagnostic materials (cytology slides, histology slides, and/or X-rays) of all subjects develop-

ing cancer were reviewed and the diagnosis of cancer confirmed by an International Endpoints Review Committee composed of expert cytologists, pathologists, and radiologists from the United States and China.³ These follow-up procedures were used through the end of May 1991, 42–43 months after the endoscopy examinations.

Analysis

In this survey, 754 of the 833 subjects who underwent endoscopy had one or more esophageal biopsies that were satisfactory for histologic diagnosis. Of these, 72 had received a diagnosis of cancer (of any site) before or during the 1987 endoscopy exams. The analytic cohort for this study consisted of the remaining 682 subjects who had at least one satisfactory squamous cell biopsy and who were free of cancer at the beginning of the follow-up period.

The age, sex, smoking status (ever smoked regularly ≥ 6 months), and alcohol use (any drinking of alcohol during the last 12 months) were recorded by questionnaire at the time of endoscopy. The pretrial cytologic diagnoses (Dysplasia 1 [low grade], Dysplasia 2 [high grade]) came from balloon cytology examinations performed in 1983.¹¹

For each subject, a worst esophageal diagnosis was determined using the hierarchy of invasive cancer greater than carcinoma in situ greater than dysplasia greater than esophagitis greater than acanthosis greater than basal cell hyperplasia greater than normal. The subjects' worst esophageal diagnoses were then compared with the occurrence of squamous cell carcinoma of the esophagus, other cancers, and death through May 1991.

Descriptive statistics of the follow-up results were generated based on all subjects in the analytic cohort, with deletions as necessary for missing data. Age-specific esophageal cancer incidence rates for each of the histologic categories were calculated by determining the number of cases that had occurred in each age and histologic category and dividing that number by the number of person-years of observation in that category. Rates were age-adjusted using the 1987 age distribution of all subjects in the analytic cohort as weights. Relative risks and confidence intervals for the histologic categories (modeled as indicator variables with normal as the reference) were estimated by Cox models using SAS PHREG¹² with adjustment for age (continuous variable), sex, smoking, alcohol use, 1983 cytologic diagnosis, and treatment group (dichotomous variables).

Results

Table 1 shows the association between the subjects' worst 1987 esophageal biopsy diagnoses and other po-

tential risk factors for esophageal cancer. There was little variation in age across the diagnostic categories, but subjects with dysplasia or carcinoma in situ were more likely to be male, to smoke, to have a 1983 cytologic diagnosis of Dysplasia 2, and to be in the placebo treatment group than were subjects with normal mucosa. The small differences in treatment group assignment are unlikely to have influenced the follow-up results, because treatment did not significantly affect esophageal cancer incidence or mortality in the overall trial.⁴

Table 2 shows the relationship between endoscopic appearance and biopsy diagnosis for the 1389 esophageal biopsy specimens from subjects in the analytic cohort. Overall, 70% of the biopsies were taken from focal lesions. The proportion of biopsies taken from these sites increased with increasing severity of biopsy diagnosis, reaching 95%, 97%, and 100% for moderate dysplasia, severe dysplasia, and carcinoma in situ, respectively. Endoscopic descriptions of the biopsy sites were not sufficiently detailed to reliably subdivide the focal lesions.

Fifty-two new cases of esophageal cancer were diagnosed in the analytic cohort during the follow-up period, including 9 cases in the first year, 6 in the second year, 27 in the third year, and 10 in the first half of the fourth year. All of the esophageal cancers were squamous cell carcinomas.

Table 3 shows the relationship between the 1987 esophageal biopsy diagnoses and esophageal cancer incidence during the subsequent 3.5 years. Very few subjects with normal mucosa and none with a worst-biopsy diagnosis of acanthosis or esophagitis developed esophageal cancer in the follow-up period. In contrast, 5% of those with basal cell hyperplasia or mild dysplasia, 27% of those with moderate dysplasia, and 67% of those with severe dysplasia or carcinoma in situ developed esophageal cancer during this time. The cumulative incidence for subjects originally classified as dysplasia not otherwise specified was 33%, consistent with this category being a mix of all grades of dysplasia. The age-adjusted rates and relative risks for developing esophageal cancer paralleled the cumulative incidence figures. Relative to those with normal mucosa, only the subjects with initial biopsies showing moderate dysplasia, severe dysplasia, or carcinoma in situ had significantly elevated risk. The relative risk estimates after multivariate adjustment did not differ greatly from those after age- and sex-adjustment. Exclusion of cases diagnosed in the first year after endoscopy did not significantly change the multivariate-adjusted relative risk estimates (basal cell hyperplasia = 2.5, mild dysplasia = 2.0, moderate dysplasia = 14.2, severe dysplasia = 75.2, dysplasia not otherwise specified = 19.6, and carcinoma in situ = 68.2).

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Table 1. Subject Characteristics, by Worst 1987 Esophageal Biopsy Diagnosis

Variable	Worst 1987 esophageal biopsy diagnosis									Total
	Normal	BCH	Acanthosis	Esophagitis	mD	MD	SD	NOS	CIS	
No. of subjects	375	40	77	33	76	30	23	12	16	682
Age in 1987 (mean) (yr)	55	55	57	54	56	56	56	56	56	55
Sex (male) (%)	35	48	53	30	43	50	39	58	56	40
Smoking (regularly \geq 6 mo) (%)	20	27	33	16	18	31	18	50	44	23
Alcohol use (any) (%)	20	18	21	9	12	27	14	17	19	18
Cytology in 1983 (dysplasia 2) (%)	54	45	49	58	70	50	70	50	69	55
Treatment (active) (%)	53	45	58	61	45	47	52	33	56	52

BCH: basal cell hyperplasia; mD: mild dysplasia; MD: moderate dysplasia; SD: severe dysplasia; NOS: dysplasia not otherwise specified; CIS: carcinoma in situ.

In addition to the 52 squamous cell carcinoma of the esophagus, there were 22 gastric adenocarcinomas (including 21 from the gastric cardia) and one liver cancer diagnosed in the analytic cohort during the follow-up period, but there was no association between the occurrence of these tumors and the 1987 esophageal biopsy diagnoses. There were 6 esophageal cancer deaths, 1 gastric cancer death, 1 liver cancer death, and 22 non-cancer deaths during the follow-up period. There were too few cancer deaths for analysis; there was no association between the noncancer deaths and the 1987 esophageal biopsy diagnoses.

Discussion

Crespi et al. and Munoz et al.¹³⁻¹⁵ described high prevalences of histologic esophagitis, atrophy, and dysplasia in Iranian and Chinese populations that have high esophageal cancer rates and little or no evidence of esophageal reflux. Based on differences in the prevalence of these lesions between high and low risk populations and a 1-year follow-up study of 20 patients, they proposed that esophagitis, atrophy, and dysplasia may be precursor lesions of esophageal cancer in these populations.^{14,15} Using similar methods, Yang and Qiu^{16,17} found essentially equal prevalences of esophagitis and atrophy in high and low risk Chinese populations but found higher prevalences of basal cell hyperplasia and

dysplasia in their high risk group. They also found progression to cancer in 34% of subjects whose initial biopsy results showed esophagitis and dysplasia but similar progression in only 4% of those with esophagitis alone, leading them to suggest that dysplasia is the primary precancerous lesion in the high risk areas of China.^{16,17} More recently, using somewhat different histologic criteria, we observed a low prevalence of esophagitis and no cases of atrophy in an endoscopic survey of persons participating in the Linxian nutrition intervention trials,⁶ causing us to further question the role of these lesions as precursors of esophageal cancer in this population. The current evaluation was a 3.5 year follow-up study of the subjects in this 1987 endoscopic survey.

In our analysis, none of the 33 subjects with a worst 1987 diagnosis of esophagitis developed esophageal cancer within the subsequent 3.5 years. In contrast, 42 (27%) of the 157 subjects with an initial diagnosis of dysplasia or carcinoma in situ were found to have esophageal cancer during this interval, and increasing grades of dysplasia were associated with dramatically increasing risk. Moderate and severe dysplasia and carcinoma in situ were the only histologic lesions associated with a significantly increased risk of squamous cell carcinoma of the esophagus within the 3.5-year follow-up period. The combined sensitivity of all grades of dysplasia (and carcinoma in situ) for the development of

Table 2. Correlation of Endoscopic Appearance and Biopsy Diagnosis in the 1987 Endoscopic Survey

Endoscopic appearance	Esophageal biopsy diagnosis									Total
	Normal	BCH	Acanthosis	Esophagitis	mD	MD	SD	NOS	CIS	
Focal lesion	620 (63)	51 (81)	72 (79)	33 (77)	85 (84)	40 (95)	31 (97)	20 (100)	16 (100)	968 (70)
No focal lesion	361 (37)	12 (19)	19 (21)	10 (23)	16 (16)	2 (5)	1 (3)	0 (0)	0 (0)	421 (30)
Total	981	63	91	43	101	42	32	20	16	1389

BCH: basal cell hyperplasia; mD: mild dysplasia; MD: moderate dysplasia; SD: severe dysplasia; NOS: dysplasia not otherwise specified; CIS: carcinoma in situ. Values are no. of biopsies (column percent).

Table 3. Incidence and Relative Risk of Squamous Cell Carcinoma of the Esophagus During 1987-1991, by Worst 1987 Esophageal Biopsy Diagnosis

Variable	Worst 1987 esophageal biopsy diagnosis									
	Normal	BCH	Acanthosis	Esophagitis	mD	MD	SD	NOS	CIS	Total
No. of subjects	375	40	77	33	76	30	23	12	16	682
Cumulative incidence*	8 (2.1%)	2 (5.0%)	0 (0.0%)	0 (0.0%)	4 (5.3%)	8 (26.7%)	15 (65.2%)	4 (33.3%)	11 (68.8%)	52 (7.6%)
Incidence rates†	645	1761	0	0	1229	11616	30419	10062	28087	2274
Age- and sex-adjusted RR‡	1.0	2.3 (0.5-10.8)	—	—	2.5 (0.7-8.2)	14.3 (5.3-38.2)	55.6 (23.4-132.1)	19.9 (5.9-67.2)	53.5 (21.0-136.6)	—
Multivariate-adjusted RR§	1.0	2.1 (0.4-9.8)	—	—	2.2 (0.7-7.5)	15.8 (5.9-42.2)	72.6 (29.8-176.9)	22.9 (6.7-78.0)	62.5 (24.1-161.9)	—

BCH: basal cell hyperplasia; mD: mild dysplasia; MD: moderate dysplasia; SD: severe dysplasia; NOS: dysplasia not otherwise specified; CIS: carcinoma in situ.

* Number (percent) of subjects with each 1987 biopsy result who developed esophageal cancer during 1987-1991.

† Esophageal cancer incidence rates (per 100,000 person-years) for 1987-1991, adjusted to the age distribution of the analytic cohort (< 50 yr = 22.4%, 50-59 yr = 46.0%, ≥ 60 yr = 31.5%).

‡ Relative risk (95% confidence interval) of esophageal cancer incidence during 1987-1991, adjusted for age and sex.

§ Relative risk (95% confidence interval) of esophageal cancer incidence during 1987-1991, adjusted for age, sex, smoking, alcohol use, 1983 cytology diagnosis, and treatment group.

|| Reference category.

squamous cancer was 42/52 (81%), and the combined specificity of these diagnoses for this outcome was 515/630 (82%). There was no association between initial esophageal biopsy diagnoses and the development of cancer in other organs or the occurrence of noncancer death.

One possible explanation for the striking relative risks associated with moderate and severe dysplasia and carcinoma in situ in our study could be that the endoscopic biopsies in these cases missed invasive disease that was already present. Although such sampling error cannot be excluded, it seems unlikely that it significantly affected our results, because 43 of 52 (83%) of the esophageal cancer cases were diagnosed more than 1 year after the endoscopic survey, and exclusion of cases diagnosed within the first year did not significantly affect the relative risk estimates.

Forty subjects in the current analysis had basal cell hyperplasia (without elongated lamina propria papillae or other abnormality) as their worst 1987 biopsy finding. The risk of these subjects developing squamous cell carcinoma was greater than that of subjects with normal mucosa and was similar to that of subjects with mild dysplasia. This is consistent with evidence suggesting that basal cell hyperplasia may sometimes have neoplastic potential, at least in high risk populations. As mentioned earlier, Yang and Qiu found a higher prevalence of basal cell hyperplasia in high risk than in low risk Chinese populations,^{16,17} and several authors have found increased amounts and expanded distributions of epithelial proliferation in biopsies of basal cell hyperplasia from high risk groups.^{18,19} Perhaps our categories of basal cell hyperplasia and mild dysplasia include a

mix of cases with and without neoplastic potential, and we may need more sensitive ways than routine histologic studies to distinguish which cases will progress.

In the current study, subjects with initial biopsy diagnoses of severe dysplasia and carcinoma in situ had virtually identical rates and risks of subsequent squamous cell carcinoma of the esophagus. This strongly suggests that the separation of severely dysplastic biopsies into two categories based on incomplete versus complete involvement of the upper third of the epithelium is a clinically irrelevant distinction that should be abandoned. Indeed, our overall findings suggest a continuous spectrum of esophageal intraepithelial neoplasia, without morphologically distinguishable "dysplasia" and "in situ carcinoma." We think it is time to consider alternative classification schemes for esophageal squamous precursor lesions, including those analogous to the three-grade (cervical intraepithelial neoplasia) or two-grade (squamous intraepithelial lesion) classifications used for squamous cell precancerous lesions of the cervix.

The follow-up interval in this analysis was 3.5 years. Information about progression to cancer within this period should be useful for identifying patients who may benefit from increased clinical surveillance or focal therapy. Longer follow-up will be necessary, however, to identify less severe conditions that predispose to cancer but that take longer than 3.5 years to show their effect. Such information may be important for our understanding of esophageal carcinogenesis and for helping us design useful long term cancer prevention strategies in high risk populations. For example, if additional follow-up shows an elevated risk for Linxian sub-

jects with biopsy-proven esophagitis relative to those with normal mucosa, interventions that reduce the prevalence of esophagitis in this population may be useful in long term cancer control.

Besides information about the identity of precancerous conditions, the current data also provide two kinds of evidence suggesting that these neoplastic lesions are endoscopically visible in the Linxian population. First, in the 1987 survey, nearly all of the biopsies showing moderate dysplasia, severe dysplasia, and carcinoma in situ came from endoscopically identified focal lesions. This close association was also found in a subsequent, more detailed endoscopic study from Linxian, in which 81% of moderately dysplastic or worse biopsy specimens (and only 6% of normal biopsies) came from visibly abnormal sites described as friability, focal red area, erosion, plaque, or nodule, and 94% of patients with moderate dysplasia or worse diagnoses would have been identified if only these target lesions had been sampled.²⁰

The second kind of evidence suggesting the endoscopic visibility of precancerous squamous lesions is the follow-up results themselves: In 1987, the endoscopic biopsies sampled only a small fraction of the esophageal mucosa. For this sampling to achieve such a high correlation between squamous dysplasia and subsequent cancer, either the dysplasia must have been diffuse throughout the mucosa, so that a biopsy anywhere would capture it, or, if focal, the dysplasia must have been visualized in some way and targeted for biopsy. Previous mapping studies have shown that squamous dysplasia is usually a focal or multifocal process in the esophagus.²¹⁻²⁴ Thus, the high correlation seen in this follow-up study implies that squamous dysplasia of the esophagus in this population is usually associated with endoscopically visible lesions.

The current study was performed in a population with an extraordinary risk for developing esophageal cancer. Our results may or may not be applicable to lower risk populations.

In summary, we performed a prospective follow-up study to examine the relationship between esophageal squamous cell biopsy diagnoses and subsequent development of squamous cell carcinoma of the esophagus in a high risk Chinese population. We found that moderate and severe dysplasia and carcinoma in situ were the only histologic lesions associated with a significantly increased risk of developing this cancer within 3.5 years after endoscopy. Increasing grades of dysplasia were associated with increasing risk, but severe dysplasia and carcinoma in situ identified similar degrees of risk, findings that suggest a continuous spectrum of esophageal intraepithelial neoplasia and argue against a concept of morphologically distinguishable dysplasia

and in situ carcinoma. Longer follow-up should provide additional information about the role of other diagnostic categories that may take more than 3.5 years to affect the occurrence of squamous cell carcinoma of the esophagus in this population.

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