

Esophageal Cytology and Subsequent Risk of Esophageal Cancer

A Prospective Follow-up Study from Linxian, China

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This paper reports a 15-year follow-up study of 12,693 persons in Linxian, China, who were originally screened by esophageal balloon cytology in 1974. The purpose of the study was to evaluate the ability of esophageal balloon cytology to identify individuals at increased risk for developing esophageal cancer. Age, sex and cytologic diagnoses were obtained from the original 1974 records, and information on vital status, cancer experience and potential confounding risk factors was collected from interviews and medical abstracts in 1989. A total of 1,162 incident cases of esophageal cancer and 993 deaths due to esophageal cancer were identified and used in this analysis. The follow-up study showed that the risk of esophageal cancer incidence and mortality increased in parallel with the presumed severity of the 1974 Chinese cytologic diagnoses. After adjusting for potential confounding factors, the relative risks (and 95% confidence intervals) for esophageal cancer incidence, by cytologic diagnosis, were: normal, 1.00; esophagitis, 1.52 (1.07–2.14); hyperplasia, 1.17 (1.02–1.33); dysplasia 1, 1.53 (1.10–2.14); dysplasia 2, 1.89 (1.47–2.41); and suspicious for cancer, 5.77 (3.79–8.80). These results suggest that esophageal balloon cytology, as performed and interpreted in Linxian in 1974, successfully identified individuals at increased risk for esophageal cancer. (Acta Cytol 38:183–192, 1994)

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The Taihang mountain area of northern China has some of the highest recorded esophageal cancer mortality rates in the world. In Linxian, Henan Province, the age-adjusted mortality rates for esophageal cancer in 1973-1975 were 161 per 100,000 for men and 103 per 100,000 for women, and by age 75 there was a cumulative mortality from esophageal cancer of over 20% for both sexes.^{5,7} Esophageal cancer has been an important cause of death in this area for hundreds of years.⁵

Symptomatic esophageal cancer is difficult to cure by surgery, radiotherapy or chemotherapy, alone or in combination. Five-year survival rates are among the lowest for any cancer.¹⁰ Over the past 35 years, Chinese scientists have conducted two main kinds of research in an attempt to control esophageal cancer before it reaches a symptomatic stage. One research method has utilized epidemiologic studies, aimed at identifying harmful exposures that might be lessened or removed. These studies have led to many etiologic hypotheses and several public health interventions, although the principal causes of the clustering of elevated cancer mortality remain to be clarified.^{6,7,16} The other research method has been the development and use of esophageal balloon cytology (là wǎng) screening, aimed at detecting surgically curable precancerous and early cancerous lesions. This method has been commonly used in parts of China for diagnosing symptomatic patients and for screening asymptomatic, high-risk populations.

The study reported here was a 15-year follow-up of an esophageal balloon cytology mass population screening of 13,808 persons that was conducted in Linxian in 1974. The purpose of the study was to quantify prospectively the ability of esophageal balloon cytology in this setting to identify people at high risk of developing esophageal cancer.

Materials and Methods

The 1974 Mass Screening

In August 1974, scientists from the Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS), Beijing, and Henan Medical University (HMU), Zhengzhou, jointly known as the Coordinating Group for Research on Esophageal Carcinoma, conducted population-based esophageal balloon cytology screening in Yaocun Commune, Linxian, Henan Province. At that time the population of Yaocun Commune over 30 years of age was approximately 26,000, and all those people were invited to participate. Symptoms, family history,

prior history of cancer or other factors were not considered in the invitation to potential participants. Teams of cytopathologists, cytotechnologists and other medical workers went from village to village and performed the balloon cytology study, using standard collection methods¹⁵; 13,808 subjects (7,025 males and 6,783 females) participated in the screening. The smears were stained with Papanicolaou stain and read under the direction of Dr. Qiong Shen, HMU, and Dr. Yi-Jing Shu, CICAMS. Data recorded for each subject in 1974 included name, sex, age, cytologic diagnosis, and an identification number. These data were keypunched in 1989 from the original 1974 record book in Yaocun Commune.

Cytologic Categories

The cytologic categories and criteria used in the 1974 screening, listed in order of presumed increasing severity, were as follows. (The terms in parentheses are the Chinese diagnoses recorded in 1974, some of which have been grouped as shown for analysis.)

- Normal (zhèng cháng) (Figure 1). Most cells were normal intermediate cells, with 10-15% normal superficial cells. Rare parabasal cells could be present.
- Esophagitis (shí guǎn yán) (Figure 2). Normal cells were found in association with a significant number of inflammatory cells. Inflammatory cells infiltrating sheets of epithelial cells could be seen.
- Hyperplasia (qīng dù zēng shēng) (Figure 3).

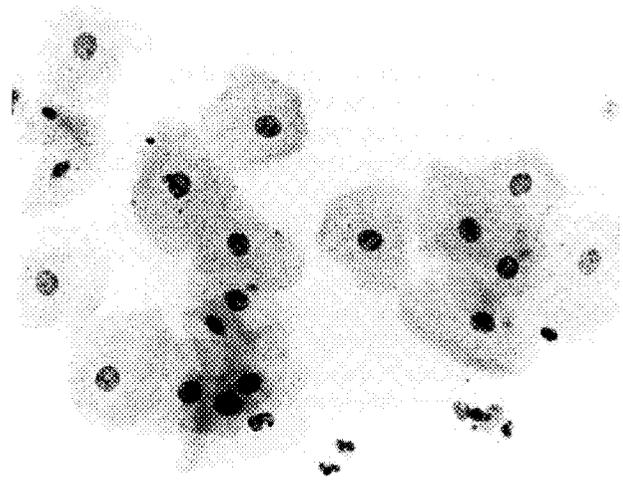


Figure 1
Normal smear. Intermediate cells predominate, but a few superficial cells are also present (Papanicolaou stain, $\times 400$).

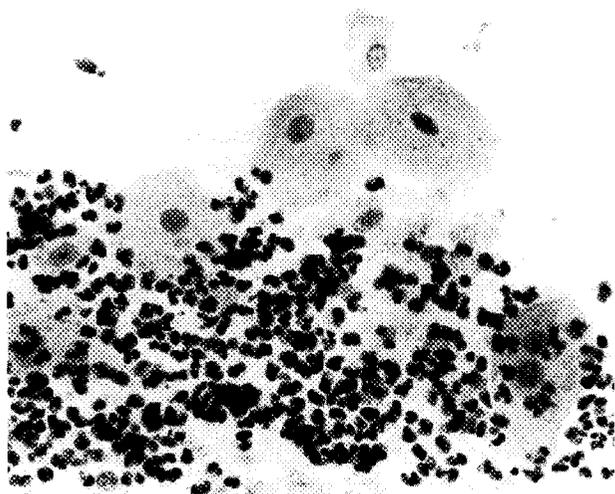


Figure 2
Esophagitis. Normal epithelial cells are accompanied by many inflammatory cells (Papanicolaou stain, $\times 400$).

The nuclei were mildly hyperchromatic and enlarged but less than three times the size of nuclei in normal cells from the same epithelial layer.

- Dysplasia 1 (zhōng dù zēng shēng; zhòng dù zēng shēng yī jí) (Figure 4). The nuclei were hyperchromatic, with finely granular and evenly distributed chromatin. The nuclei were between three and four times the size of nuclei in normal cells from the same epithelial layer. Dysplastic parabasal cells were sometimes increased in number. At least five

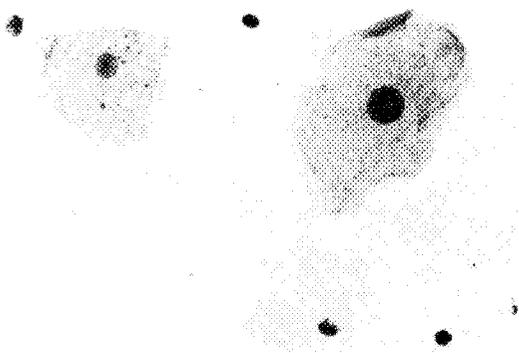


Figure 3
Hyperplasia. The nucleus of the hyperplastic cell (upper right) is enlarged but less than three times the size of the nucleus of the normal intermediate cell (upper left). The chromatin is finely granular and evenly distributed (Papanicolaou stain, $\times 400$).

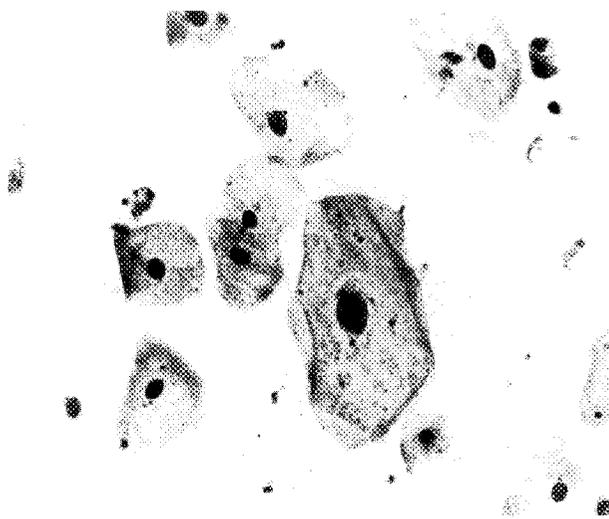


Figure 4
Dysplasia 1. The nucleus is three to four times the size of a normal intermediate cell nucleus (Papanicolaou stain, $\times 400$).

cells meeting the criteria for dysplasia 1 were present in the sample.

- Dysplasia 2 (zhòng dù zēng shēng; zhòng dù zēng shēng èr jí) (Figure 5). The pattern was similar to dysplasia 1 except that the abnormal nuclei were more than four times the size of nuclei in normal cells from the same epithelial layer. At least five dysplasia 2 cells were present in the smears. Malignant tumor cells were absent.

- Suspicious for cancer (kě yí ái) (Figure 6). The

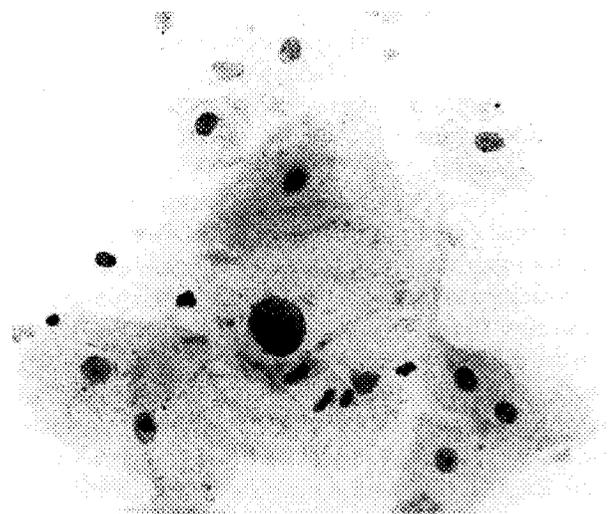


Figure 5
Dysplasia 2. The nucleus is more than four times the size of a normal intermediate cell nucleus (Papanicolaou stain, $\times 400$).

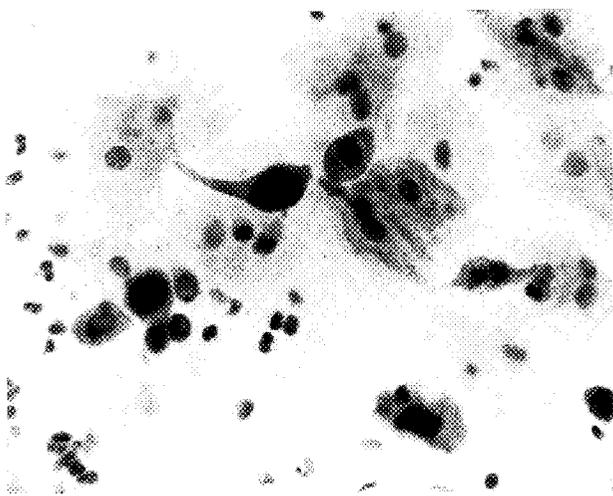


Figure 6
Suspicious for cancer. There are spindle-shaped squamous cells with enlarged, hyperchromatic nuclei but no typical cancer cells (Papanicolaou stain, $\times 400$).

cytologist was suspicious but not certain that cancer was present. This usually occurred when there were many dysplasia 2 cells or spindle-shaped squamous cells, without malignant tumor cells, or when rare cells were found with some atypical nuclear features but more abundant cytoplasm than is usually seen in malignant tumor cells.

- Cancer (ái; lín ái; xiàn ái) (Figure 7). Malignant tumor cells were present. The nuclei exhibited coarse and irregular chromatin structures that varied in size. They sometimes had irregularly thickened and contoured nuclear envelopes. The nuclear/cytoplasmic ratio was increased. Nucleoli could be present. (Nucleoli were seen only occasionally in squamous cancer; they were always seen in adenocarcinoma.)

The cancers diagnosed in the 1974 screening were subcategorized as squamous cell carcinoma, adenocarcinoma or carcinoma not otherwise specified. All the other diagnoses were cytologic categorizations of squamous cells. Abnormalities of glandular cells other than cancer were not recorded.

Additional descriptions and illustrations of Chinese esophageal cytologic categories can be found in previous publications.^{2,3,13-15} A description of the historical development of these categories and their English translations can be found in the Appendix. In this paper, we have used the most common current translations for the three grades of *zēng shēng*. We have also used the terms *esophagitis* (*shí guǎn yán*) (not thought to be a precancerous

condition in 1974) and *suspicious for cancer* (*kě yí ái*) because they were used in the 1974 screening.

The Follow-up Study

In the follow-up study we attempted to interview all subjects who participated in the 1974 mass screening. If a subject had died or moved away from Linxian, his or her closest available relative was interviewed. The interviews were performed by a team of 20 trained interviewers in the three-month period from November 1988 through January 1989. The interviewers were individually introduced to the subjects by their village doctor, and interviews were carried out in the subjects' homes. The interview obtained demographic information and included questions on vital status, cancer experience, smoking, alcohol consumption, diet, drinking water source, socioeconomic variables and family history of cancer.

In 1989, 13,610 interviews were performed, representing 98.6% of the 13,808 subjects screened in 1974. Sixty-eight percent of the interview respondents were the subjects who were screened in 1974, 12% were spouses of the subjects, 17% were other relatives, and 3% were nonrelatives. To check the reproducibility of the interview results, 1,007 (7.4%) of the subjects were randomly selected and reinterviewed a month after the original interview.

Medical records were sought for all interviewed subjects with evidence of any type of cancer or a record of death from any cause. A team of four

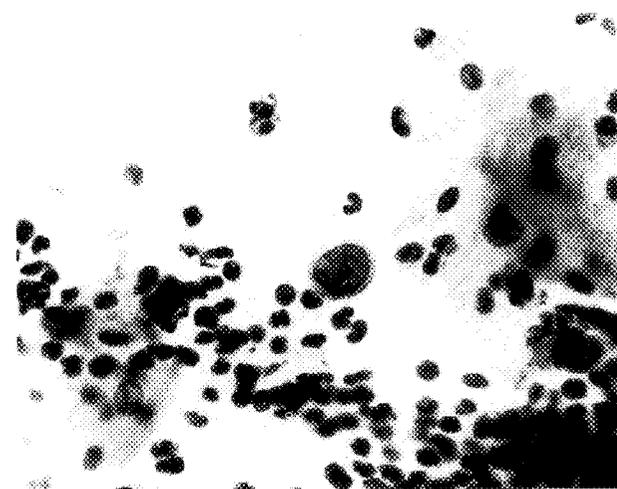


Figure 7
Cancer. This malignant tumor cell has coarse, irregularly distributed chromatin, a large nuclear/cytoplasmic ratio and a nucleolus (Papanicolaou stain, $\times 630$).

trained abstractors used hospital records and death certificates to obtain information on vital status, cancer type, date and method of diagnosis of cancer, date of death and cause of death. Death certificate information came from the Linxian Esophageal Cancer Institute. For patients with medical records, the date of the first admission with a cancer diagnosis was considered to be the cancer incidence date. For patients with only death certificate data available, the date of death was considered to be the cancer incidence date. Medical abstracts were obtained on 80% of both incident and mortal cases of esophageal cancer.

Accuracy of the interview data was checked by comparing interview and reinterview responses and by comparing interview and medical abstract data for questions that appeared in both sources. The concordance between interview and reinterview responses was high: 100% for vital status and type of incident cancer (esophageal cancer versus other cancers) and >95% for year of death (± 2 years), cause of death (cancer versus other causes or esophageal cancer versus other causes) and most smoking, alcohol, dietary, socioeconomic and family history-related questions. The concordance between interview and medical abstract data was also high: >99% for vital status and >95% for type of cancer, year of death and cause of death. When the same question appeared in both interview and abstract files, the response in the abstract file was used for analysis.

Throughout this paper the term *esophageal cancer* includes both esophageal and gastric cardia cancers. Cancers arising in the gastric cardia have symptoms similar to those arising in the lower esophagus, and both tumors have traditionally been called esophageal cancer in Linxian. This tradition was reflected in the 1989 interview answers, medical records and death certificates, so accurate separation of these tumors could not be made with data from these sources. The tumor cell type of the incident cancers was available only rarely. In addition, it is not known how many of the cancers reported during follow-up were intraepithelial and how many were invasive since both conditions were classified as cancer and the presence or absence of invasion was not recorded.

Analysis

To analyze the ability of the esophageal balloon cytology technique in the 1974 screening to identify people at high risk of developing esophageal can-

cer, we compared the subjects' 1974 cytologic diagnoses with their subsequent vital status and cancer experience identified in the 1989 interviews and medical abstracts.

Of the 13,610 interviewed subjects, 619 had technically unsatisfactory cytology smears, and 298 others had received a diagnosis of esophageal cancer before or during the 1974 screening. The analytic cohort for this study consisted of the 12,693 interviewed subjects who had a satisfactory balloon cytology examination in 1974 and were free of cancer at the beginning of the follow-up period.

Risk factor information obtained from the interview in 1989 and used in these analyses included: ever smoked cigarettes regularly for six months or longer (no/yes), ever drank alcoholic beverages at least once daily for six months or longer (no/yes), consumption of pickled vegetables in 1974 (never/ever), regular consumption of moldy food in 1974 (no/yes), history of cancer of the esophagus or stomach in spouse, parent, sibling or children (no/yes), highest level of formal education as of 1974 (none/any) and primary source of drinking water prior to 1974 (well/surface).

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 and mortality rates for each of the 1974 cytologic categories were calculated by determining the number of cases that had occurred in each age and cytologic category and dividing that number by the number of person-years of observation in that category. Rates were calculated separately for males, females and combined and were age adjusted using the age distribution in 1974 of the entire population of interviewed subjects as weights. Relative risks for the cytologic categories (modeled as indicator variables, with normal as the reference) were calculated using SAS PROC PHGLM (SAS, Inc., Cary, North Carolina, U.S.A.)¹¹ with adjustment for age (continuous variable), sex (dichotomous variable) and other risk factor variables as described above. Confidence intervals of the regression coefficients were estimated assuming normal distributions of the estimates of the coefficients.

Results

In the 1974 balloon screening examination, 13,166 (95.4%) of the 13,808 subjects had technically satisfactory cytology smears. Tables I and II show the cytologic diagnoses of these 13,166 subjects, strati-

Table I Results of 1974 Balloon Cytology Screening Examinations in Yaocun Commune, Linxian, China, by Age Group

Age (yr)	1974 Cytologic category							Total
	Normal	Esophagitis	Hyperplasia	Dysplasia 1	Dysplasia 2	Suspicious for cancer	Cancer	
< 30	328 (61.4) ^a	14 (2.6)	176 (33.0)	8 (1.5)	7 (1.3)	0 (0.0)	1 (0.2)	534 (100)
30-39	2,258 (53.0)	101 (2.5)	1,570 (38.6)	98 (2.4)	120 (2.9)	8 (0.2)	16 (0.4)	4,071 (100)
40-49	1,810 (45.8)	89 (2.3)	1,730 (43.7)	101 (2.6)	159 (4.0)	25 (0.6)	41 (1.0)	3,955 (100)
50-59	1,304 (42.5)	91 (3.0)	1,327 (43.2)	93 (3.0)	160 (5.2)	20 (0.7)	74 (2.4)	3,069 (100)
60+	569 (37.0)	32 (2.1)	707 (46.0)	56 (3.6)	78 (5.1)	12 (0.8)	83 (5.4)	1,537 (100)
All	6,169 (46.9)	327 (2.5)	5,510 (41.8)	356 (2.7)	524 (4.0)	65 (0.5)	215 (1.6)	13,166 (100)

^aNumber of subjects (row percent).

fied by age (Table I) and gender (Table II). About half the subjects had normal cytology. Among those with abnormalities, hyperplasia was by far the most common. With increasing age, the percentage of subjects with normal cytology decreased, and that of subjects with hyperplasia, dysplasia 1, dysplasia 2, suspicious for cancer and cancer increased (Table I). This age pattern within cytology categories and the distribution of cytology results within age categories were similar for male and female subjects, so only the combined results are shown. Overall, normal cytology was slightly more common in males than in females, and the diagnoses of esophagitis, hyperplasia, dysplasia 1, dysplasia 2 and cancer were slightly more common in females than in males (Table II).

Tables III-V are based on the analytic cohort of 12,693 subjects. Table III shows the association of the 1974 cytology results with other potential esophageal cancer risk factors. The differences in prevalence of these factors among the cytology groups were typically small, but all the tested variables except daily alcohol and family history showed a significant χ^2 association with the cytologic categories. Assessment of the association with alcohol was limited because of the very low prevalence of daily use. Prominent trends paralleling the severity of cytologic diagnoses were seen only with increasing age and lack of education. Information

on the relationship between these and other factors and the development of esophageal cancer during the follow-up period can be found in a companion paper by Yu et al.¹⁷

Tables IV and V show the relationship between the 1974 cytology results and later esophageal cancer experience. A total of 1,162 new cases of esophageal cancer and 993 deaths from esophageal cancer occurred in the analytic cohort during the 15-year follow-up period. In addition to esophageal cancer deaths, this cohort experienced 246 deaths due to other cancers and 1,491 deaths due to noncancer causes.

Table IV shows incidence data for the follow-up period by initial cytologic diagnosis, including the total number of new esophageal cancer cases, age-adjusted esophageal cancer incidence rates by gender, and age- and sex-adjusted and multivariate-adjusted relative risks for developing esophageal cancer. Table V shows similar data for esophageal cancer mortality. For both incidence and mortality, the cumulative number of events, the age-adjusted rates and the relative risks all increased with the presumed severity of the 1974 cytologic diagnoses, except that the rates and risks for subjects with a 1974 diagnosis of esophagitis were higher than those for subjects with a diagnosis of hyperplasia and were similar to the rates and risks associated with a diagnosis of dysplasia 1. Male incidence and

Table II Results of 1974 Balloon Cytology Screening Examinations in Yaocun Commune, Linxian, China, by Gender

Gender	1974 Cytologic category							Total
	Normal	Esophagitis	Hyperplasia	Dysplasia 1	Dysplasia 2	Suspicious for cancer	Cancer	
Male	3,206 (48.3) ^a	153 (2.3)	2,732 (41.1)	166 (2.5)	254 (3.8)	33 (0.5)	101 (1.5)	6,645 (100)
Female	2,963 (45.4)	174 (2.7)	2,778 (42.6)	190 (2.9)	270 (4.1)	32 (0.5)	114 (1.8)	6,521 (100)
All	6,169 (46.9)	327 (2.5)	5,510 (41.8)	356 (2.7)	524 (4.0)	65 (0.5)	215 (1.6)	13,166 (100)

^aNumber of subjects (row percent).

Table III Association of 1974 Cytology Results with Other Potential Esophageal Cancer Risk Factors

Variable ^a	1974 Cytologic category						P value ^b
	Normal	Esophagitis	Hyperplasia	Dysplasia 1	Dysplasia 2	Suspicious for cancer	
Age in 1974 (yr)	44	45	46	47	48	50	
Sex (male)	52%	47%	50%	47%	48%	51%	< .01
Ever smoke	35%	30%	32%	30%	31%	32%	< .01
Daily alcohol	1%	1%	1%	1%	1%	0%	.84
Eat pickled vegetables	66%	72%	66%	67%	60%	67%	.03
Eat moldy foods	22%	28%	24%	26%	24%	33%	< .01
Positive family history of cancer	29%	32%	29%	30%	27%	24%	.74
Any formal education	59%	55%	54%	51%	49%	45%	< .01
Well water	90%	70%	90%	94%	90%	88%	< .01

^aSee methods for a detailed description of the variables.

^bP values are based on χ^2 values from 2 × 6 contingency tables.

mortality rates were greater than female rates for all cytologic categories. Age-specific incidence and mortality rates (not shown) showed increasing rates with increasing age for both males and females in all cytologic categories. The relative risks after multivariate adjustment did not differ greatly from those after age and sex adjustment.

There was no association between 1974 diagnoses and death due to causes other than esophageal cancer. (Age- and sex-adjusted relative risks for these deaths combined were: normal, 1.00; esophagitis, 0.93; hyperplasia, 1.00; dysplasia 1, 1.09; dysplasia 2, 0.93; and suspicious for cancer, 0.56.)

Discussion

A gastric balloon cytology technique was first

described by Panico, Papanicolaou and Cooper in 1950,⁹ and an adaptation of this technique for sampling the esophagus was reported by Bruinsma in 1957.¹ In the late 1950s and early 1960s, Chinese scientists developed this technique further and expanded its use in an effort to control esophageal cancer in high-risk areas of northern China. Initially, only symptomatic hospitalized patients were screened. While the yield of cancer cases was high, most of the cases were too advanced to be resectable. Next, the technique was taken to villages, where everyone with symptoms of abnormal swallowing or a family history of esophageal cancer was invited to be screened. Again, quite a few cancer cases were identified, but most were unresectable. Finally, in the 1970s, mass screenings of all

Table IV Esophageal Cancer Incidence During 1974-1989, by 1974 Cytology Results

Variable	1974 Cytologic category						Total
	Normal	Esophagitis	Hyperplasia	Dysplasia 1	Dysplasia 2	Suspicious for cancer	
No. of subjects	6,070	318	5,411	338	496	60	12,693
Cumulative incidence ^a	449 (7.4%)	37 (11.6%)	530 (9.8%)	43 (12.7%)	79 (15.9%)	24 (40.0%)	1,162 (9.2%)
Male rates ^b	822	1,173	915	1,321	1,333	4,194	917
Female rates ^b	521	930	658	833	1,042	3,031	636
Total rates ^b	682	1,022	792	1,028	1,196	3,480	784
Age- and sex-adjusted relative risk ^c	1.00	1.56 (1.12-2.18)	1.20 (1.05-1.36)	1.62 (1.18-2.21)	1.82 (1.43-2.32)	5.84 (3.87-8.80)	<i>P</i> for trend < .001
Multivariate-adjusted relative risk ^d	1.00	1.52 (1.07-2.14)	1.17 (1.02-1.33)	1.53 (1.10-2.14)	1.89 (1.47-2.41)	5.77 (3.79-8.80)	<i>P</i> for trend < .001

^aNumber (percent) of subjects with each 1974 cytology result who developed esophageal cancer during 1974-1989.

^bEsophageal cancer incidence rates (per 100,000 person-years) for 1974-1989, adjusted to the age distribution of all 1974 screened subjects (< 30 years = 4%, 30-39 years = 31%, 40-49 years = 30%, 50-59 years = 23%, 60+ years = 12%).

^cRelative risk (95% confidence interval) of esophageal cancer incidence during 1974-1989, adjusted for age and gender.

^dRelative risk (95% confidence interval) of esophageal cancer incidence during 1974-1989, adjusted for age, gender, smoking, alcohol, pickled vegetables, moldy foods, family history, education and water source.

Table V Esophageal Cancer Mortality During 1974-1989, by 1974 Cytology Results

Variable	1974 Cytologic category						Total
	Normal	Esophagitis	Hyperplasia	Dysplasia 1	Dysplasia 2	Suspicious for cancer	
No. of subjects	6,070	318	5,411	338	496	60	12,693
Cumulative mortality ^a	389 (6.4%)	33 (10.4%)	447 (8.3%)	37 (11.0%)	69 (13.9%)	18 (30.0%)	993 (7.8%)
Male rates ^b	727	1,041	765	1,062	1,241	2,144	787
Female rates ^b	450	824	548	730	771	2,126	537
Total rates ^b	599	903	663	865	1,007	2,104	670
Age- and sex-adjusted relative risk ^c	1.00	1.58 (1.11-2.26)	1.14 (0.99-1.30)	1.57 (1.12-2.21)	1.76 (1.36-2.27)	3.73 (2.31-6.01)	<i>P</i> for trend < .001
Multivariate-adjusted relative risk ^d	1.00	1.58 (1.10-2.28)	1.10 (0.96-1.27)	1.47 (1.02-2.11)	1.80 (1.38-2.35)	3.77 (2.31-6.17)	<i>P</i> for trend < .001

^aNumber (percent) of subjects with each 1974 cytology result who died of esophageal cancer during 1974-1989.

^bEsophageal cancer mortality rates (per 100,000 person-years) for 1974-1989, adjusted to the age distribution of all 1974 screened subjects (<30 years = 4%, 30-39 years = 31%, 40-49 years = 30%, 50-59 years = 23%, 60+ years = 12%).

^cRelative risk (95% confidence interval) of esophageal cancer mortality during 1974-1989, adjusted for age and gender.

^dRelative risk (95% confidence interval) of esophageal cancer mortality during 1974-1989, adjusted for age, gender, smoking, alcohol, pickled vegetables, moldy foods, family history, education and water source.

villagers over the age of 30, with or without symptoms or a family history, were begun. The total yield of cancer cases was lower than before, but the proportion of cases that were resectable was significantly higher.¹³⁻¹⁵

Esophageal balloon screening has two related but separable purposes: to identify people with resectable esophageal cancer and to identify people who do not currently have esophageal cancer but are at increased risk of developing it in the future. Previous reports have documented the ability of esophageal balloon cytology in China to identify resectable "early esophageal cancer" (defined as carcinoma *in situ* or cancer that has invaded no deeper than the submucosa) in symptomatic and asymptomatic patients.¹³⁻¹⁵ The focus of the present study was to evaluate the ability of esophageal balloon cytology to identify persons without current cancer who are at increased risk of developing it in the future.

The results of the current follow-up study show a convincing relationship between the 1974 cytologic diagnoses and subsequent esophageal cancer experience. Both rates and relative risks of esophageal cancer incidence and mortality during the follow-up period paralleled the presumed severity of the 1974 cytologic diagnoses. The diagnosis of hyperplasia conveyed only marginally increased risks of developing or dying from esophageal cancer, but diagnoses of esophagitis, dysplasia 1, dysplasia 2 and suspicious for cancer carried significant and progressively increasing risks. The risks associated with esophagitis and dysplasia 1 were approxi-

mately equal. The difference in risks between these diagnoses and dysplasia 2 was small, but the difference in risks between dysplasia 2 and suspicious for cancer was large.

The one unexpected finding in this study was that esophagitis, which was not considered a precancerous condition in 1974, was associated with an increased risk of esophageal cancer that was equivalent to that for dysplasia 1. Unlike all other cytologic categories associated with increased esophageal cancer risk, however, the prevalence of esophagitis did not increase with age. Esophagitis was diagnosed in only 2.5% of the 1974 subjects and was not a category recorded in later balloon cytology screenings in Linxian.^{4,8,12}

Thirty-nine percent (449 of 1,162) of the incident esophageal cancers reported during the follow-up period occurred in subjects with normal cytology in the 1974 examination. While most of these cases probably developed both precancerous lesions and cancer after the 1974 examination, there may also have been cases with false-negative initial cytologic diagnoses, caused by incomplete mucosal sampling or inaccurate reading. Also noteworthy are the relatively low proportions of subjects with initial cytologic diagnoses of dysplasia 1 (13%), dysplasia 2 (16%) and suspicious for cancer (40%) who developed clinical esophageal cancer in the subsequent 15 years. Factors that may have contributed to these low progression rates include false-positive cytologic diagnoses, regression of dysplastic lesions, a latency period > 15 years before the onset of clini-

cally apparent disease and incorrect classification of evident disease or cause of death by the sources we used for follow-up data.

The cytologic categories and criteria used in the 1974 screening were developed and have been used almost exclusively in China, and they have not yet been carefully compared with the cytologic criteria most commonly used in other parts of the world. Examination of the correlation of Chinese cytologic diagnoses with histologic findings in biopsies or resection specimens is also incomplete. Additional studies are needed in both areas.

The results of this study are similar to those of the two previously published follow-up studies of esophageal balloon cytology screenings in northern China.^{4,8} Both studies followed participants of a 1975 mass screening in Shen Guan Commune, Linxian. In the first study,⁴ 17,898 subjects initially free of cancer were followed by interviews nine years after the screening; the cumulative incidence of esophageal cancer in subjects with initial cytologic diagnoses of normal, hyperplasia and dysplasia were 3.4%, 4.7% and 10.1%. In the second study,⁸ 958 subjects without cancer were followed by periodic medical examinations and medical record abstracts for 11 years; the relative risks for esophageal cancer incidence in persons with cytologic diagnoses of normal, hyperplasia and dysplasia were 1.00, 1.02, and 2.39 (2.90 after age-adjustment).

The results of the current study suggest that esophageal balloon cytology, as performed and interpreted at the Yaocun Commune in 1974, successfully identified people at increased risk of developing esophageal cancer and correctly identified some relative degrees of increased risk. The additional finding that the cytologic diagnoses did not correlate with deaths due to causes other than esophageal cancer implies some specificity of these diagnoses for esophageal cancer.

The overall results of a follow-up study of this type depend on many factors, including the ability of the balloon technique to fully sample the esophageal mucosa, the ability of the cytologic criteria to identify and logically categorize precancerous lesions, the ability of cytopathologists and cytotechnologists to accurately apply the cytologic criteria, the ability of those interviewed to remember past events and accurately identify the symptoms of esophageal cancer, and the accuracy of diagnostic techniques used and recorded in the abstracted medical records. All these (and other) factors offer possibilities of error. However, even in this com-

plex setting, the results of this study appear to show clearly that the balloon cytology procedure was effective in identifying people at high risk of developing esophageal cancer.

Appendix

During the past 40 years, cytologists inside and outside China have had little interaction, and somewhat different cytologic criteria and traditions of cytologic categorization have developed. In the early 1960s, when Chinese cytologists began using esophageal balloon cytology to look for cases of esophageal cancer, cases were diagnosed only as "cancer" (ái) or "not cancer" (fēi ái), based on a comparison of the cytologic features seen in smears with those seen in tissue sections of resected carcinomas. Within a few years, an intermediate category (zēng shēng) was introduced for cases that lacked typical malignant cells but contained cells with some abnormal nuclear features. It was noted that similar atypical cells were often seen associated with malignant tumor cells in smears from proven cases of cancer. Unfortunately, the Chinese term zēng shēng was translated several ways in English-language publications, including "atypia,"⁸ "dyskaryosis,"² "hyperplasia"⁷ and "dysplasia,"^{3,15} leading to confusion among those trying to understand and compare Chinese results in translation.

Over time, the Chinese term zēng shēng was divided into several categories, or grades. First, it was divided into two grades, qīng dù zēng shēng ("light" zēng shēng) and zhòng dù zēng shēng ("heavy" zēng shēng), based primarily on finding abnormal cells with nuclei less than or greater than three times the size of normal nuclei. These two grades were translated as "mild" and "severe" hyperplasia, as "hyperplasia" and "dysplasia" or as "mild hyperplasia" and "dysplasia 2," depending on the emphasis of different authors. Zēng shēng, literally "increased birth," was most logically translated into English as "hyperplasia," and qīng dù (light) zēng shēng and zhòng dù (heavy) zēng shēng could logically be translated as mild and severe hyperplasia. Chinese cytologists recognized, however, that patients with smaller nuclei were at less risk of developing esophageal cancer than were those with larger nuclei, and some cytologists who understood the prognostic implications of the two grades and of the English terms *hyperplasia* (usually not associated with increased cancer risk) and *dysplasia* (usually considered a precancerous condition) preferred to translate qīng dù zēng shēng as "hyperplasia" (or

mild hyperplasia) and zhòng dù zēng shēng as "dysplasia" (or severe dysplasia). They thought that this was a more correct translation in terms of prognostic meaning.

Later, zēng shēng was divided into three grades: those emphasizing the continuum of morphologic abnormalities used the terms qīng dù zēng shēng ("light" zēng shēng), zhōng dù zēng shēng ("middle" zēng shēng), and zhòng dù zēng shēng ("heavy" zēng shēng), translated as "mild," "moderate" and "severe" hyperplasia; those emphasizing the prognostic implications of the categories used the terms qīng dù zēng shēng, zhòng dù zēng shēng yī jí ("heavy zēng shēng first degree") and zhòng dù zēng shēng èr jí ("heavy zēng shēng, second degree"), translated as mild hyperplasia, severe dysplasia group I and severe dysplasia group II. In both systems the division between the first and second grades was based on finding abnormal cells with nuclei less than or greater than three times the size of normal nuclei. Finally, additional precancerous categories, such as "suspicious for cancer" (kě yí ái) and "near cancer" (jìn ái), were sometimes added between the three grades of zēng shēng and cancer.

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