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ESOPHAGEAL BALLOON CYTOLOGY AND SUBSEQUENT RISK OF ESOPHAGEAL AND GASTRIC-CARDIA CANCER IN A HIGH-RISK CHINESE POPULATION

S.F. LIU[1], Q. SHEN[2], S.M. DAWSEY[3,6], G.Q. WANG[1], R.K. NIEBERG[5], Z.Y. WANG[1], M. WEINER[5], B. ZHOU[1], J. CAO[1], Y. YU[1], W.D. GUO[1], J.Y. LI[1], W.J. BLOT[4], B. LI[1] and P.R. TAYLOR[3]

[1]*Cancer Institute, Chinese Academy of Medical Sciences, Beijing;* [2]*Henan Medical University, Zhengzhou, Henan Province, People's Republic of China;* [3]*Cancer Prevention Studies Branch and* [4]*Biostatistics Branch, National Cancer Institute, Executive Plaza North, Room 211, 9000 Rockville Pike, Bethesda, MD 20892; and* [5]*UCLA School of Medicine, Los Angeles, CA 90024, USA.*

Linxian, China has some of the highest rates of esophageal/gastric cardia cancer in the world. In 1983, esophageal balloon cytology screening was performed in 3 communes in northern Linxian. Of the participants, 10,066 with no evidence of cancer were followed prospectively for 7½ years to evaluate the ability of the initial cytologic diagnoses to identify individuals at increased risk for developing cancer of the esophagus or gastric cardia. A total of 747 incident cases of esophageal or cardia cancer and 322 deaths due to these tumors were identified during the follow-up period and used in this analysis. The risks for esophageal or cardia cancer incidence and mortality increased in parallel with the presumed severity of the 1983 Chinese cytologic diagnoses. After adjusting for potential confounding factors, relative risks for esophageal or cardia cancer incidence, by initial cytologic diagnosis, were normal = 1.00 (reference), hyperplasia = 1.25, dysplasia 1 = 2.20, dysplasia 2 = 4.22 and near-cancer = 5.96. Our results suggest that esophageal balloon cytology, as performed and interpreted in Linxian in 1983, successfully identified individuals at increased risk for developing cancer of the esophagus or gastric cardia.
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Linxian, China, has some of the highest rates of esophageal/gastric cardia cancer in the world. Because of similar symptomatology, both of these tumors have traditionally been called "esophageal cancer" in Linxian. During 1973–1975, the annual age-adjusted mortality rates for "esophageal cancer" in Linxian were 161/100,000 for men and 103/100,000 for women, and by age 75 the cumulative mortality from these cancers was over 20% in both sexes. Esophageal/gastric cardia cancer has been an important cause of death in this region for hundreds of years (Li *et al.*, 1980; Li, 1982).

Since the late 1950s, Chinese scientists have developed esophageal balloon cytology (là wǎng) screening as an early detection technique for identifying surgically curable precancerous and early cancerous lesions of the esophagus and gastric cardia (Shen and Shu, 1982; Shu, 1983, 1985; Shen, 1984). In 1983, balloon-cytology screening of 12,877 adult residents was performed in 3 northern communes of Linxian as a baseline study for 2 nutrition intervention trials (Li *et al.*, 1993; Shen *et al.*, 1993). This report describes a 7½-year follow-up of the 10,066 subjects from this cytology screening who were free of cancer in 1983 and who were followed prospectively in these intervention trials. The purpose of this analysis was to evaluate the ability of the cytologic diagnoses to identify people at increased risk of developing esophageal or gastric cardia cancer.

MATERIAL AND METHODS

Balloon-cytology screening

In November and December, 1983, scientists from the Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS) in Beijing and from Henan Medical University (HMU) in Zhengzhou conducted a population-based esophageal balloon-cytology screening in Yaocun, Rencun and Donggang communes in Linxian, Henan Province. All inhabitants of these 3 communes between the ages of 40 and 69 were invited to participate, without regard for symptoms, family history or other factors. Teams of cytopathologists, cytotechnologists and other medical workers went from village to village and performed the balloon-swallow examinations, using standard collection methods (Shu, 1983). The smears were stained with Papanicolaou stain and were read under the direction of Dr. Qiong Shen of HMU and Dr. Shu-Fan Liu of CICAMS, who personally reviewed all diagnoses of dysplasia, near-cancer or cancer. Data recorded for each subject included name, gender, age, birthdate, an identification number, and the cytologic diagnosis. The cytologic results of the 1983 screening have been previously reported (Shen *et al.*, 1993).

Cytologic categories

There were 6 cytologic categories for squamous and for columnar cells used in the 1983 screening. The category names and the defining nuclear criteria were the same for both cell types; the identification of squamous or columnar cell type was based on cytoplasmic characteristics. The cytologic categories and criteria, listed in order of presumed increasing severity, were as follows: Normal (zhèng cháng): most cells are normal intermediate cells, with 10 to 15% normal superficial cells. Rare parabasal cells may be present. Hyperplasia (qīng dù zēng shēng): the nuclei are mildly hyperchromatic and enlarged, being 2 or more but less than 3 times the size of nuclei in normal intermediate cells. Dysplasia 1 (zhòng dù zēng shēng yī jí): the nuclei are hyperchromatic, with finely granular and evenly distributed chromatin. The nuclei are 3 or more but less than 4 times the size of the nuclei of normal intermediate cells. When hyperplasia cells are present in the smear, finding a single cell meeting the criteria for dysplasia 1 is sufficient for this diagnosis. Dysplasia 2 (zhòng dù zēng shēng èr jí): the pattern is similar to dysplasia 1 except that the abnormal nuclei are 4 or more but less than 5 times the size of the nuclei of normal intermediate cells. When hyperplasia or dysplasia 1 cells are present in the smear, finding a single dysplasia 2 cell is sufficient for this diagnosis. Near-cancer (jìn ái): the pattern is similar to dysplasia 2, except that the abnormal nuclei are 5 or more times the size of the nuclei of normal intermediate cells. Finding a single near-cancer cell is sufficient for this diagnosis. Typical cancer cells are absent. Cancer (ái; lín ái; xiàn ái): typical cancer cells are present. Typical cancer cells have coarse chromatin granules which vary in size and are irregularly distributed. They may have irregularly thickened and irregularly contoured nuclear membranes. The nuclear-cytoplasmic (N/C) ratio is increased. Nucleoli may be present

[6]To whom correspondence and reprint requests should be addressed.

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(nucleoli are seen only occasionally in squamous cancer; they are always seen in adenocarcinoma).

Additional descriptions and illustrations of Chinese esophageal cytologic categories can be found in previous publications (Shen and Shu, 1982; Shu, 1983, 1985; Shen, 1984; Shen *et al.*, 1993; Dawsey *et al.*, 1994). A description of the historical development of these categories and their English translations can be found in Dawsey *et al.* (1994).

Follow-up procedures

Follow-up data were collected prospectively through 1991 on all subjects from the 1983 screening who participated in either of the Linxian nutrition intervention trials. Those who had a 1983 diagnosis of dysplasia 1 or dysplasia 2 were enrolled in the dysplasia trial, while those with 1983 diagnoses of normal, hyperplasia or near-cancer entered the general population trial. These two trials, described in detail elsewhere (Li *et al.*, 1993), differed in design and in the treatments received, but had similar surveillance for symptomatic cancers and deaths. All medical facilities, including commune hospitals, the Linxian County Cancer Hospital, and the cancer hospital in the prefecture capital of Anyang, notified trial investigators of all cancer diagnoses among residents of the communes in the trials. Participants with cancer symptoms and those who died from any cause were identified by village doctors on their monthly visits to deliver the intervention pills. Additional visits to look for symptomatic individuals 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 subjects were referred to this field station or their commune hospital for further evaluation.

In addition to these procedures, cytologic and endoscopic examinations were carried out in 1987 and 1991, 4 years and 7½ years after the 1983 cytology screening, to look for asymptomatic cancers (Li *et al.*, 1993). The 1987 examinations were performed only in the dysplasia trial; 78% of the subjects in the current analysis with a 1983 diagnosis of dysplasia 1 or dysplasia 2 participated in this cytology screening, and 30% underwent endoscopy. None of the subjects with a 1983 diagnosis of normal, hyperplasia or near-cancer participated in these 1987 screening exams. The 1991 examinations, performed both in the dysplasia and in the general population trials, included subjects from the full spectrum of 1983 diagnoses: 19% of the subjects in the current analysis who had normal cytology in 1983 participated in the 1991 cytology screening, as did 22% of those with hyperplasia, 64% with dysplasia 1, 59% with dysplasia 2, and 21% with near-cancer; 2% of the subjects who had normal cytology in 1983 participated in the 1991 endoscopy examinations, as did 4% of those with hyperplasia, 13% with dysplasia 1, 11% with dysplasia 2, and 0% with near-cancer.

Case records and diagnostic materials (cytology slides, histology slides and/or X rays) of all subjects developing cancer were reviewed and the diagnosis of cancer confirmed by an International Endpoints Review Committee composed of expert cytologists, pathologists and radiologists from the US and China (Li *et al.*, 1993). These follow-up procedures were used through the end of May, 1991, 7½ years after the 1983 balloon cytology screening examination.

Analysis

In the 1983 screening, 12,877 subjects had cytology slides which were satisfactory for diagnosis. Of these, 309 received a diagnosis of cancer during the screening. Of the remaining 12,568 subjects, 10,066 participated in the Linxian nutrition intervention trials. The analytic cohort for this study consisted of these 10,066 subjects who had satisfactory cytology diagnoses in 1983, who were free of cancer at the beginning of the follow-up period, and who were followed prospectively through 1991 in the nutrition intervention trials.

To analyze the ability of the 1983 esophageal balloon-cytology screening to identify people at increased risk of developing or dying from esophageal or gastric cardia cancer, we compared the subjects' worst 1983 cytology diagnosis with their subsequent vital status and esophageal- and cardia-cancer incidence and mortality during the follow-up period. The squamous and columnar cytologic diagnoses were combined for analysis, since it was not clear how accurately these cell types were separated in 1983. The 1983 screening was the first large cytologic examination in Linxian in which columnar diagnoses less severe than adenocarcinoma were recorded (Shen *et al.*, 1993; Dawsey *et al.*, 1994), and only 11% of the subjects received columnar diagnoses (Shen *et al.*, 1993). While this low proportion may in part have reflected poor sampling of the upper stomach by the balloon, it may also have been an indication that cytoplasmic differentiation of the cells was not always clear and that the readers assumed that abnormal cells were squamous unless there was definite evidence of glandular origin. In addition, normal columnar cells may not have been considered important and thus not recorded when they were a minority of the cells present.

Risk-factor information obtained from intervention-trial baseline interviews conducted in 1984 (dysplasia trial) or 1985 (general population trial) and used in this analysis included: ever smoked cigarettes regularly for 6 months or longer (no/yes); consumption of alcoholic beverages during the past 12 months (rarely or never/ ≥ a few times/year); family history of cancer in parents, siblings, spouse or children (no/yes); highest level of formal education (none/any); drinking water piped into home or courtyard (no/yes); and consumption of the following during the past 12 months: moldy food (never/ever), pickled vegetables (never/ever), fresh vegetables (< 2×/day/ ≥ 2×/day), fresh fruit (< 1×/month/ ≥ 1×/month), and meat (pork, beef, rabbit, chicken or duck) (< 1×/month/ ≥ 1×/month).

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 cytologic categories were calculated by determining the number of cases which 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 and females and for both sexes combined, and were age-adjusted using the age distribution in 1983 of all screened subjects as weights. Relative risks and confidence intervals for the cytologic categories (modeled as indicator variables with normal as the reference) were estimates by Cox models using SAS PROC PHREG (SAS Institute, 1985) with adjustment for age (continuous), gender, smoking, alcohol use, family history of cancer, formal education, drinking-water source, and consumption of pickled vegetables, moldy foods, fresh vegetables, fresh fruits, and meat (dichotomous variables), and treatment group. Treatment group was modelled in a variety of ways: as 2 indicator variables (any treatment, no treatment); as 8 mutually exclusive indicator variables based on the pills received (general population trial supplements AB, AC, AD, BC, BD, CD, ABCD; dysplasia trial active pills); and as 5 indicator variables based on the vitamin/mineral supplement factors received (general population trial factors A, B, C, D; dysplasia trial active pills). The results were virtually identical with each of these models. The model with 8 mutually exclusive indicator variables was chosen for the final multivariate regressions, because it resulted in the most conservative risk estimates. Cancer-risk trends across the 1983 diagnoses were tested by

scoring the cytologic categories 0 to 4 as previously described and including this variable in Cox model regressions.

To examine potential bias due to higher screening rates in subjects with 1983 diagnoses of dysplasia 1 and 2, age- and gender-adjusted relative risks were estimated before and after exclusion of all cancer cases diagnosed during the 1987 and 1991 cytologic and endoscopic screening examinations.

RESULTS

Table I shows the association of the 1983 cytology results with selected *a priori* esophageal or gastric-cardia cancer-risk factors (Li *et al.*, 1989; Yu *et al.*, 1993). There was a steady increase in age with increasing severity of the cytologic categories. Subjects with dysplasia were more likely to be female and to have a family history of cancer and were less likely to smoke, to use alcohol, or to eat fresh vegetables, fresh fruits or meat than were subjects with normal mucosa.

Tables II and III show the relationship between the 1983 cytology results and later esophageal and gastric-cardia cancer experience. A total of 747 new cases of esophageal or cardia cancer and 322 deaths from these tumors occurred in the analytic cohort during the 7½-year follow-up period. In addition to esophageal and gastric-cardia cancer deaths, this cohort experienced 86 deaths due to other cancers (including 34 non-cardia stomach cancers) and 433 deaths due to non-cancer causes.

Table II shows incidence data for the follow-up period by initial cytologic diagnosis, including cumulative incidence, age-adjusted rates by gender, age-, and gender- adjusted relative risks and multivariate-adjusted relative risks. Table III shows similar data for mortality. For incidence and for mortality, the number of events, rates and relative risks all increased with the presumed severity of the 1983 cytologic diagnoses. Male incidence and mortality rates were greater than female rates for all cytologic categories. The relative risks after multivariate adjustment did not differ greatly from those after adjustment for age and gender. Age- and gender-adjusted relative risks for esophageal and gastric-cardia cancer incidence continued to show a progression of risk with increasing severity of initial cytologic diagnosis after exclusion of cases diagnosed during the 1987 and 1991 cytologic and endoscopic screening examinations: normal, 1.00; hyperplasia, 1.32 (1.00–1.72); dysplasia 1, 1.93 (1.47–2.52); dysplasia 2, 3.92 (2.89–5.32); and near-cancer, 7.15 (3.58–14.25).

There was no association between 1983 diagnoses and death due to causes other than esophageal or gastric-cardia cancer: age- and gender-adjusted relative risks for these deaths combined were normal, 1.00; hyperplasia, 1.03; dysplasia 1, 1.13; dysplasia 2, 0.93; and near-cancer, 1.12.

TABLE I – ASSOCIATION OF 1983 CYTOLOGY RESULTS AND OTHER POTENTIAL RISK FACTORS FOR ESOPHAGEAL OR GASTRIC-CARDIA CANCER

Variable[1]	All subjects	1983 cytology category[2]				
		N	H	D1	D2	NC
Number of subjects	10066	2949	3645	2364	800	38
Age in 1983 (mean)	51	49	51	52	52	55
Gender (male)	47%	48%	48%	46%	40%	55%
Smoking (regularly ≥ 6 months)	32%	34%	34%	30%	25%	32%
Alcohol use (≥ few ×/yr)	23%	26%	24%	19%	17%	11%
Family history of cancer (+)	40%	36%	38%	43%	48%	39%
Formal education (any)	57%	58%	55%	58%	55%	55%
Water piped into home (yes)	14%	15%	14%	12%	12%	16%
Moldy food (≥ 1 ×/yr)	18%	17%	18%	20%	17%	18%
Pickled vegetables (≥ 1×/yr)	9%	7%	8%	11%	9%	5%
Fresh vegetables (≥ 2×/d)	63%	72%	72%	46%	42%	58%
Fresh fruit (≥ 1×/month)	32%	38%	34%	26%	22%	29%
Meat (≥ 1×/month)	31%	34%	31%	29%	27%	37%

[1]See "Material and Methods" for a detailed description of the variables.–[2]N, normal; H, hyperplasia; D1, dysplasia 1; D2, dysplasia 2; NC, near-cancer.

TABLE II – ESOPHAGEAL AND GASTRIC-CARDIA CANCER INCIDENCE DURING 1983–1991, BY WORST 1983 CYTOLOGY DIAGNOSIS

	1983 cytology category					Total
	Normal	Hyperplasia	Dysplasia 1	Dysplasia 2	Near-cancer	
Number of subjects	2949	3645	2634	800	38	10,066
Cumulative incidence[1]	117 (4.0%)	187 (5.1%)	279 (10.6%)	154 (19.3%)	10 (26.3%)	747 (7.4%)
Male rates[2]	607	750	1612	3199	6525	1102
Female rates[2]	417	486	926	1820	1253	714
Total rates[2]	512	617	1236	2337	3854	897
Age- and gender-adjusted RR[3]	1.00[5]	1.23 (.98–1.55)	2.55 (2.05–3.17)	5.00 (3.92–6.37)	5.79 (3.03–11.07)	*p* for trend <.001
Multivariate-adjusted RR[4]	1.00[5]	1.25 (.99–1.56)	2.20 (1.56–3.11)	4.22 (2.93–6.08)	5.96 (3.11–11.42)	*p* for trend <.001

[1]Number (percent) of subjects with each 1983 cytology result who developed esophageal or gastric-cardia cancer during 1983–1991.–[2]Combined esophageal and gastric-cardia cancer incidence rates (per 100,000 person-years) for 1983–1991, adjusted to the age distribution of all 1983 screened subjects (< 40 yrs, 4.4%; 40–49 yrs, 35.7%; 50–59 yrs, 40.7%; 60+ yrs, 19.2%).–[3]Relative risk (95% confidence interval) of esophageal or gastric-cardia cancer incidence during 1983–1991, adjusted for age and gender.–[4]Relative risk (95% confidence interval) of esophageal or gastric-cardia cancer incidence during 1983–1991, adjusted for age, gender, smoking, alcohol use, family history, education, water source, consumption of moldy foods, pickled vegetables, fresh vegetables, fresh fruits, and meat, and treatment group.–[5]Reference category.

TABLE III – ESOPHAGEAL AND GASTRIC-CARDIA CANCER MORTALITY DURING 1983–1991, BY WORST 1983 CYTOLOGY DIAGNOSIS

	1983 cytology category					Total
	Normal	Hyperplasia	Dysplasia 1	Dysplasia 2	Near-cancer	
Number of subjects	2949	3645	2634	800	38	10,066
Cumulative mortality[1]	61 (2.1%)	92 (2.5%)	107 (4.1%)	58 (7.3%)	4 (10.5%)	322 (3.2%)
Male rates[2]	332	323	638	1121	1287	470
Female rates[2]	189	233	262	534	401	261
Total rates[2]	263	282	434	765	847	363
Age- and gender-adjusted RR[3]	1.00[5]	1.12 (0.81–1.55)	1.72 (1.26–2.36)	3.18 (2.21–4.56)	3.44 (1.25–9.49)	*p* for trend <.001
Multivariate-adjusted RR[4]	1.00[5]	1.15 (0.83–1.60)	1.53 (0.92–2.54)	2.72 (1.58–4.67)	3.46 (1.25–9.58)	*p* for trend <.001

[1]Number (percent) of subjects with each 1983 cytology result who died of esophageal or gastric-cardia cancer during 1983–1991.–[2]Combined esophageal and gastric-cardia cancer mortality rates (per 100,000 person-years) for 1983–1991, adjusted to the age distribution of all 1983 screened subjects (<40 yrs, 4.4%; 40–49 yrs, 35.7%; 50–59 yrs, 40.7%; 60+ yrs, 19.2%).–[3]Relative risk (95% confidence interval) of esophageal or gastric-cardia cancer mortality during 1983–1991, adjusted for age and gender.–[4]Relative risk (95% confidence interval) of esophageal or gastric-cardia cancer incidence during 1983–1991, adjusted for age, gender, smoking, alcohol use, family history, education, water source, consumption of moldy foods, pickled vegetables, fresh vegetables, fresh fruits, and meat, and treatment group.–[5]Reference category.

TABLE IV – AGE- AND GENDER-ADJUSTED RELATIVE RISKS FOR INCIDENT CANCERS DURING 1983–1991, BY 1983 CELL-TYPE-SPECIFIC CYTOLOGY DIAGNOSIS

	1983 squamous diagnoses (N = 9917)				
Cancer site	Normal[1]	Hyperplasia	Dysplasia 1	Dysplasia 2	Near-cancer
Esophagus (N = 429)	1.00	1.63 (1.18–2.27)	3.34 (2.45–4.57)	7.30 (5.21–10.21)	11.15 (5.29–23.54)
Gastric cardia (N = 308)	1.00	1.05 (.76–1.45)	1.84 (1.35–2.50)	2.44 (1.65–3.61)	1.81 (.44–7.43)
	1983 columnar diagnoses (N = 1087)				
Cancer site	Normal[1]	Hyperplasia	Dysplasia 1	Dysplasia 2	Near-cancer
Esophagus (N = 42)	1.00	4.05 (1.19–13.80)	9.56 (2.77–32.93)	8.48 (1.86–38.70)	—
Gastric cardia (N = 50)	1.00	1.16 (.43–3.14)	5.63 (2.26–14.07)	10.14 (3.66–28.10)	—

[1]Reference category.

Table IV shows separate relative risks for esophageal and cardia cancer incidence for 1983 cell-type-specific cytologic diagnoses. Both squamous and columnar diagnoses of dysplasia 1 and dysplasia 2 were associated with significantly increased risks both for esophageal cancer and for gastric-cardia cancer during the subsequent 7½ years.

DISCUSSION

Linxian, China, has some of the highest rates of esophageal/gastric-cardia cancer in the world (Li, 1982). Over the past 4 decades, Chinese scientists have conducted 2 principal kinds of research in Linxian to control the mortality of these tumors. One method has been epidemiologic studies to identify harmful exposures which might be lessened or removed. These studies have led to several etiologic hypotheses and public-health interventions, although the principal causes for the clustering of elevated cancer mortality remain to be clarified (Yang, 1980; Li *et al.*, 1989; Yu *et al.*, 1993). The other research method has been the development and use of esophageal balloon cytology (là wǎng) screening to detect surgically curable pre-cancerous and early cancerous lesions in symptomatic patients and in asymptomatic high-risk populations.

Esophageal balloon screening has 2 related but separable purposes: to identify people with resectable esophageal/gastric-cardia cancer, and to identify people who do not currently have 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 esophageal/gastric-cardia cancer in symptomatic and asymptomatic people (Shen and Shu, 1982; Shu, 1983, 1985; Shen, 1984). The focus of the present study was to evaluate the ability of this screening method to identify individuals without esophageal or gastric-cardia cancer who were at increased risk of developing these tumors in the future.

The results of this follow-up study show a convincing relationship between the 1983 cytologic diagnoses and the subsequent development of esophageal/gastric-cardia cancer. Both rates and relative risks of esophageal/gastric-cardia cancer incidence and mortality during the follow-up period paralleled the presumed severity of the 1983 cytologic diagnoses. The diagnosis of hyperplasia conveyed only marginally increased risk of developing or dying from esophageal or cardia cancer, but the diagnoses of dysplasia 1, dysplasia 2 and near-cancer carried significant and progressively increasing risks. The additional finding that the cytologic diagnoses did not correlate with deaths due to causes other than esophageal or gastric-cardia cancer implies specificity of these diagnoses for these diseases. Although the magnitude of relative risk for incident cancers among subjects with an initial diagnosis of dysplasia 1 or 2 was somewhat inflated by the additional cytologic and endoscopic screening these subjects received

TABLE V – RESULTS OF FOLLOW-UP STUDIES OF ESOPHAGEAL BALLOON-CYTOLOGY MASS SCREENINGS IN LINXIAN, CHINA

Year of screen	Number of subjects followed	Follow-up interval	Type of result[1]	Cytology diagnosis				
				Normal	Hyperplasia	Dysplasia		Other[2]
						Dysplasia 1	Dysplasia 2	
1974[3]	12693	15 yr	CI	7.4%	9.8%	12.7%	15.9%	40.0%
			RR	1.00	1.20	1.62	1.82	5.84
1975[4]	17898	11 yr	CI	3.4%	4.7%	10.1%		
1975[5]	958	9 yr	RR	1.00	1.02	2.90		
1983	10066	7.5 yr	CI	4.0%	5.1%	10.6%	19.3%	26.3%
			RR	1.00	1.23	2.55	5.00	5.79

[1]CI, cumulative esophageal and gastric cardia cancer incidence; RR, age- and gender-adjusted relative risk for esophageal or gastric-cardia cancer incidence.–[2]Suspicious for cancer (kě yī ái) in 1974; near-cancer (jìn ái) in 1983.–[3]Dawsey *et al.*, 1994.–[4]Follow-up Group, 1987.–[5]Lu *et al.*, 1988.

during the follow-up period, the progression of risk for incident cancers with increasing severity of initial cytologic diagnosis remained after exclusion of screening-identified cases, and the same progression of risk was seen in the mortality figures.

The cell-type-specific relative risks (Table IV) showed that both squamous and columnar diagnoses of dysplasia were separately associated with increased risks both for esophageal and for gastric-cardia cancers. This implies that the distinction of cell type in the 1983 diagnoses was not completely accurate and/or that the risks of developing these 2 tumors during the follow-up period were not independent.

The results of this study are similar to those of the 3 previous follow-up studies of esophageal balloon-cytology screenings in Linxian (Table V) (Follow-up Group, 1987; Lu *et al.*, 1988; Dawsey *et al.*, 1994). All of these studies included esophageal and gastric-cardia cancers in their follow-up data. Overall, they show little increase in risk of esophageal/gastric-cardia cancer following a cytologic diagnosis of hyperplasia but substantial elevation in risk for subjects with an initial diagnosis of dysplasia.

Comparison of the current results with those of the 1974 follow-up study (Dawsey *et al.*, 1994) is particularly interesting in relation to the importance of certain cytologic criteria. In 1974, at least 5 cells meeting the criteria for dysplasia 1 or dysplasia 2 had to be found in a patient's smears before a diagnosis of dysplasia was made (Shen and Shu, 1982; Shen, 1984; Dawsey *et al.*, 1994); but in 1983, finding a single dysplastic cell was sufficient to make these diagnoses (Shen *et al.*, 1993). This difference was reflected in a combined prevalence of dysplasia 1 and dysplasia 2 that was significantly higher in 1983 (27%) than in 1974 (7%). The relative risks associated with these diagnoses, however, were not reduced by this change, implying that the presence of one dysplastic cell in 1983 carried as much risk for future esophageal or gastric cancer as the presence of 5 dysplastic cells in 1974. While there are other differences between the 2 studies that may have affected their relative-risk estimates, these observations argue for the importance of finding a single dysplastic cell, and suggest that the 1983 criteria were more appropriate.

Sixteen percent (117/747) of the incident esophageal and gastric-cardia cancers reported during the follow-up period occurred in subjects with normal cytology in the 1983 examination. While most of these cases probably developed both pre-cancerous lesions and cancer after the 1983 screening, 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 (11%), dysplasia 2 (19%) and near-cancer (26%) who developed clinical esophageal or gastric-cardia cancer in the subsequent 7½ years. Factors that may have contributed to these low progression rates include false-positive cytologic diagnoses, regression of dysplastic lesions, and a latent period longer than 7½ years before the onset of clinically apparent disease.

The cytologic categories and criteria used in the 1983 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. In addition, the correlation of these cytologic diagnoses with histologic findings in biopsies or resection specimens has not yet been completely examined. Additional studies are needed in both of these areas.

In summary, we examined the ability of esophageal balloon-cytology screening to predict future development of esophageal or gastric-cardia cancer among adults in a high-risk Chinese population. The results of the 7½-year follow-up study suggest that this cytologic technique, as performed and interpreted in Linxian in 1983, successfully identified individuals at increased risk of developing these cancers.

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