

## Squamous Dysplasia and Early Esophageal Cancer in the Linxian Region of China: Distinctive Endoscopic Lesions

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**Background:** Linxian, China, has one of the highest rates of esophageal cancer in the world. To design a logical biopsy strategy for large-scale endoscopic surveys in Linxian, the aim of this study was to determine whether squamous dysplasia and early squamous cancer are associated with visible lesions that can be targeted for biopsy. **Methods:** Sixty-three Linxian patients with balloon cytological evidence of squamous dysplasia or early cancer of the esophagus had biopsy specimens taken every 4 cm and additional specimens taken from all visually abnormal areas. The appearance of the 398 biopsy sites was described, and abnormal-appearing areas were photographed. The endoscopic descriptions were then compared with the biopsy diagnoses. **Results:** Twenty-five of 31 (81%) moderately dysplastic or worse specimens (including all nine specimens of invasive cancer) came from visually abnormal sites classified as friability, focal red area, erosion, plaque, or nodule. Fifteen of 16 (94%) patients with moderate dysplasia or worse biopsy diagnoses would have been identified if only these visible target lesions had been sampled. **Conclusions:** For surveillance in this high-risk population, random biopsy specimens may be unnecessary; sampling the target lesions described appears sufficient to detect nearly all invasive cancer and most dysplasia. Awareness of these lesion appearances may also aid in earlier detection of squamous cancers of the esophagus in lower-risk populations such as those in Europe and North America.

Esophageal cancer is one of the most common fatal cancers worldwide.<sup>1</sup> Its prognosis remains poor despite advances in imaging and therapy because patients do not seek medical attention until they are symptomatic and their tumors are unresectable.

There is great geographic variation in the occurrence of esophageal cancer. Especially high-risk areas have been identified in Northern Iran,<sup>2,3</sup> the Central Asian Republics of the former Soviet Union,<sup>4</sup> Northern China,<sup>5</sup> and South Africa.<sup>6</sup> In some of these areas, over 20% of the population dies of esophageal cancer.<sup>5</sup>

The need for detection and curative therapy of precursor lesions and early-stage tumors in these populations is clear.

The accurate use of endoscopy in studying and managing precursor lesions and early-stage esophageal cancer requires a biopsy strategy that will reliably identify each patient's worst mucosal disease. If squamous dysplasia and early squamous cancer are endoscopically visible, then a few targeted biopsies should be adequate to diagnose and localize them. However, if these lesions are endoscopically invisible (as dysplasia and intramucosal adenocarcinoma can be in Barrett's esophagus<sup>7</sup>), then a larger number of systematic biopsy specimens must be taken.

The aim of the present study was to see if squamous dysplasia and early squamous cancer in subjects from a high-risk area of Northern China are associated with endoscopically visible lesions. This study was performed in the context of the Linxian Nutrition Intervention Trials<sup>8</sup> and was undertaken both to optimize the biopsy protocol for an end-of-trials endoscopic survey and to assist in developing the best strategy for future cytological and endoscopic screening programs in such high-risk areas.

### Materials and Methods

#### Endoscopic Examinations

This study was conducted in Linxian, Henan Province, a county of approximately 800,000 people with one of the highest esophageal cancer mortality rates in the world. The study protocol was approved by the Human Research Review Committee of the Cancer Institute of the Chinese Academy of Medical Sciences.

All cytological diagnoses were made by Chinese cytologists using the balloon swallow sampling technique and Chinese diagnostic criteria.<sup>9</sup> None of the subjects had symptoms indicative of esophageal carcinoma.

This is a U.S. government work. There are no restrictions on its use.

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The endoscopic examinations were performed in two phases, phase I in May 1989 and phase II in May 1990. In phase I, 30 subjects with a cytological diagnosis of squamous dysplasia in balloon cytology surveys in 1983 and/or 1987 underwent endoscopy with a Pentax EG-2900 video gastro-scope (Pentax, Orangeburg, NY), and videotapes were made of the entire esophageal mucosa using a 3/4-in videocassette recorder. In phase II, 33 subjects with a cytological diagnosis of squamous dysplasia or early cancer within the previous 2 months underwent endoscopy and still digital photographs were taken of visible lesions and other representative areas of the mucosa. The digital photographs were taken with the same endoscope used in phase I, stored in a Pentax IMS-3000 image management system computer, transported on computer disks, and printed by a Sony Mavigraph thermal printer.

Except for the time between cytological diagnosis and endoscopic examination and the method of mucosal photography, the examinations in both phases were similar. All patients underwent endoscopy by two experienced endoscopists (G.Q.W. and W.M.W.). The patients were given 5 mL of 1% tetracaine to drink 2–5 minutes before the passage of the endoscope, but they were not otherwise sedated and were alert throughout the procedure.

The esophagus and stomach were examined and described, and the locations of the lower and upper esophageal sphincters (in centimeters from the incisors) were recorded. Visual abnormalities were then individually described, and a biopsy was performed with 2.8-mm channel forceps. For focal lesions, specimens were also obtained from the adjacent, uninvolved mucosa. Systematic specimens were then taken at 4-cm intervals along the 6-o'clock wall beginning 2 cm below the squamocolumnar junction (Z line) and ending near the upper esophageal sphincter. The average number of squamous biopsy specimens was two from focal lesions and five from other (diffusely normal or irregular) mucosa.

All biopsy specimens were oriented mucosal side up on Millipore filter supports by experienced technologists. The tissues were fixed in Bouin's solution, embedded in paraffin, cut in 5- $\mu$ m sections, and stained with H&E.

### Endoscopic Categories

Consensus conferences were held after each phase, in which all investigators reviewed the recorded visual descriptions, the videotapes, and the still photographs to ensure that the visual descriptors had been used uniformly throughout the study and to appropriately group these descriptors for analysis. The categories of endoscopic appearance used for analysis as follows: normal, smooth or mildly wrinkled mucosa; irregular, diffusely irregular mucosa showing prominent wrinkling; small white patch, a focal raised or flat white patch with smooth distinct borders, usually <1 cm in diameter; friability/focal red area, contact bleeding (friability) or a flat red area not caused by mucosal contact (focal red area); erosion, a focal defect in the mucosa; and plaque/nodule, thickened, raised mucosa with ir-

regular indistinct borders and occasional shallow surface erosions.

### Histological Categories

The slides were read jointly by three pathologists (S.M.D., K.J.L., and F.S.L.) without knowledge of the patient's history or the visual endoscopic findings.

The histological criteria listed below were based on previous descriptions.<sup>10,11</sup>

**Normal.** There was a well-oriented squamous epithelium containing both a basal zone and a superficial zone with or without underlying lamina propria. There was no evidence of esophagitis, squamous dysplasia, or squamous cancer as defined below. Most specimens showed some mature squamous cells with abundant clear cytoplasm ("clear cell change") in the upper half of the epithelium, and many specimens showed such cells in the lower half as well. The nine biopsy specimens diagnosed as acanthosis (defined as an epithelium >0.5 mm thick without other abnormalities) and the specimen diagnosed as atrophy (defined as an epithelium  $\leq$ 10 cell layers thick) were analyzed with the normal specimens.

**Esophagitis.** One or more of the following criteria were present: (1) the lamina propria papillae extended into the upper third of the epithelium and the basal zone thickness was >15% of the epithelial thickness; (2) the epithelium was infiltrated by neutrophils ( $\geq$ 2 cells/tissue sections) or eosinophils ( $\geq$ 1 cell/tissue section); (3) there was a dense nonfollicular mononuclear infiltrate and/or an easily recognized infiltrate of neutrophils in the lamina propria. Esophagitis was graded as mild, moderate, or severe based on the amount of inflammation present. If only the first criterion above was present, the esophagitis was graded as mild. If histological erosion or ulceration was present, the esophagitis was graded as severe.

**Squamous dysplasia.** Nuclear atypia, loss of normal cellular 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.

**Squamous cancer.** Malignant squamous cells which had invaded through the basement membrane were present.

### Analysis

The recorded description of each squamous biopsy site was compared with the biopsy diagnosis from that site. When more than one biopsy specimen was taken at a site, the worst histological diagnosis was used as the biopsy diagnosis for that site. The results were analyzed separately by biopsy site ( $n = 398$ ) and by patient ( $n = 63$ ).

## Results

### Endoscopic Findings

The endoscopic findings are shown in the first two columns of Table 1. Representative examples are illustrated in Figures 1–11.

**Table 1.** Correlation of Endoscopic Appearances With Biopsy Diagnoses by Biopsy Site

| Endoscopic appearance     | n   | Biopsy diagnosis |             |                 |           |           |          |        |           | Cancer (%) |
|---------------------------|-----|------------------|-------------|-----------------|-----------|-----------|----------|--------|-----------|------------|
|                           |     | Normal (%)       | Esophagitis |                 | Total (%) | Dysplasia |          |        | Total (%) |            |
|                           |     |                  | Mild        | Moderate/severe |           | Mild      | Moderate | Severe |           |            |
| Normal                    | 177 | 160 (90)         | 11          | 2               | 13 (7)    | 1         | 2        | 1      | 4 (2)     | 0          |
| Irregular                 | 118 | 102 (86)         | 5           | 4               | 9 (8)     | 5         | 1        | 1      | 7 (6)     | 0          |
| Small white patch         | 42  | 33 (79)          | 6           | 1               | 7 (17)    | 1         | 0        | 1      | 2 (5)     | 0          |
| Friability/focal red area | 8   | 3 (38)           | 1           | 1               | 2 (25)    | 1         | 0        | 2      | 3 (38)    | 0          |
| Erosion                   | 34  | 14 (41)          | 3           | 3               | 6 (18)    | 3         | 2        | 5      | 10 (29)   | 4 (12)     |
| Plaque/nodule             | 19  | 2 (11)           | 1           | 0               | 1 (5)     | 4         | 3        | 4      | 11 (58)   | 5 (26)     |
| Total                     | 398 | 314 (79)         | 27          | 11              | 38 (10)   | 15        | 8        | 14     | 37 (9)    | 9 (2)      |

Normal mucosa (Figure 1) was present at 177 (44%) of the 398 biopsy sites. Mild wrinkling of the mucosa was common above the distal 3 cm of the esophagus.

Irregular mucosa (Figures 2 and 3) was seen at 118 (30%) of the biopsy sites.

Forty-two (11%) of the biopsy sites were categorized as small white patches (Figure 4). Most of these patches were <1 cm, off-white in color, smooth-bordered, and scattered on otherwise normal or irregular mucosa. Uncommonly (in one case), such patches were confluent. Another occasional variant was a chalky white patch that appeared to be stuck on the mucosa and was felt endoscopically to be adherent food.

The mucosal appearances of friability (Figure 5) and focal red area (not shown) were uncommon, each being present at only four (1%) of the biopsy sites. These two appearances were distinct because focal red areas were seen before mucosal contact, but friability was evident only after passage of the endoscope.

Thirty-four (8%) of the biopsy sites had the visual appearance of erosions. A range of erosions was seen, including linear erosions (Figures 6 and 7), small, punched-out erosions (Figure 8), and large, broad-based erosions (Figure 9).

Sixteen (4%) of the biopsy sites were categorized as plaques and three (1%) were called nodules. Both of these lesions were easily recognizable as significantly abnormal mucosa. The plaques (Figure 10) were large, thickened areas, and the nodules (Figure 11) were gross tumors protruding into the lumen.

### Histological Findings

The histological findings are shown in Tables 1 and 2. Examples of histologically normal mucosa, esophagitis, mild dysplasia, severe dysplasia, and early invasive cancer are illustrated in Figures 12–16.

Squamous specimens were obtained from 398 biopsy sites. Of the 38 biopsy sites showing esophagi-

tis, 27 (71%) were graded mild, 8 (21%) moderate, and 3 (8%) severe. Of the 37 squamous dysplasias, 15 (40%) were mild, 8 (22%) moderate, and 14 (38%) severe. Of the nine invasive cancers, seven (78%) appeared to be cases of early invasion.

Categorized by their worst biopsy diagnosis, 19 of 63 patients (30%) had normal diagnosis and 20 of 63 (32%) had esophagitis. Twenty-four of the 63 (38%) subjects had dysplasia or carcinoma; of these 24 patients, 8 (13% of 63) had mild dysplasia; 3 (5%) moderate dysplasia; 5 (8%) severe dysplasia, and 8 (13%) invasive squamous cancer.

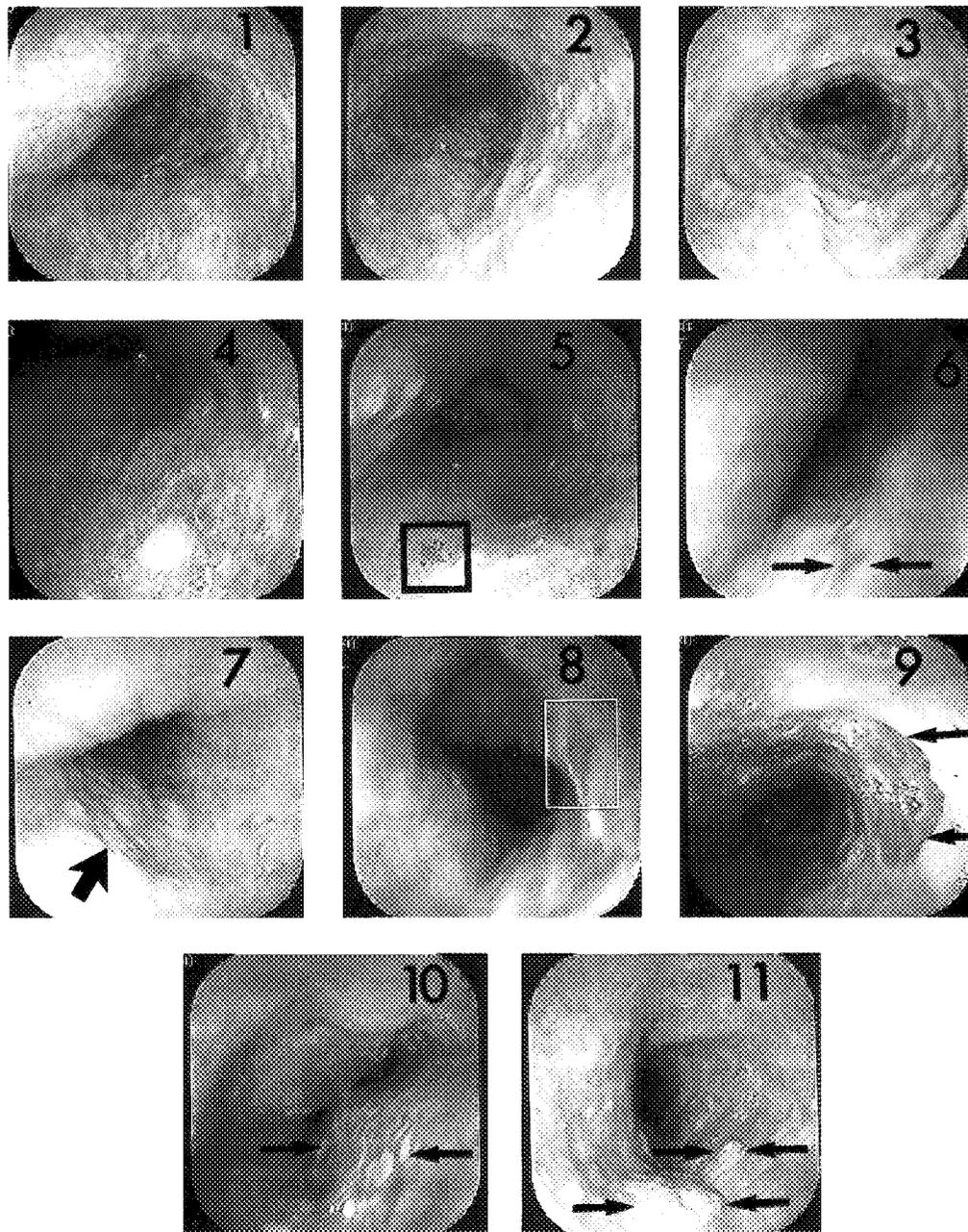
### Correlation of Visual and Histological Findings

Table 1 shows the correlation of endoscopic appearances and biopsy diagnoses by biopsy site.

The endoscopic categories of normal and irregular had similar distributions of diagnoses, with more than 85% of the specimens showing histologically normal mucosa, a few specimens showing esophagitis, rare specimens showing dysplasia, and no specimens showing invasive cancer.

Our endoscopic category of small white patch has been called leukoplakia by others and has been correlated with clear cell acanthosis in their studies.<sup>12</sup> Twenty-three (55%) of our 42 biopsy specimens of these lesions showed prominent clear cell change involving both the upper and lower halves of the epithelium, consistent with a diagnosis of clear cell acanthosis. Ten additional specimens (24%) showed esophagitis, dysplasia, and/or parakeratosis. Nine specimens (21%) showed no histological reason for a focal endoscopic lesion.

Of the 4 friable biopsy sites, 1 showed severe dysplasia, 1 mild dysplasia, 1 severe esophagitis with histological erosion, and 1 mild esophagitis. Of the 4 focal red areas, 1 site showed severe dysplasia on biopsy and 3 showed normal mucosa.



**Figure 1.** Endoscopically normal mucosa in the midesophagus. **Figure 2.** Irregular mucosa seen with full air insufflation. **Figure 3.** Irregular mucosa, same individual. With partial deflation of the lumen, circumferential ribbing becomes evident. Similar ribbing was also seen in endoscopically normal mucosa. **Figure 4.** A small white patch on an otherwise normal mucosa. **Figure 5.** Friability; subepithelial hemorrhage (box) that occurred after passage of the endoscope. **Figure 6.** Single linear erosion in the midesophagus (arrows). **Figure 7.** Multiple linear erosions (arrow). **Figure 8.** A small "cookie-cutter" erosion (box). **Figure 9.** A large broad-based erosion (arrows). **Figure 10.** A white raised plaque with shallow surface erosions (arrows). **Figure 11.** Two nodules (arrows).

Of the 34 erosions, 4 showed invasive cancer, 10 dysplasia, 6 esophagitis, and 14 normal mucosa. Still mucosal photographs were available for 19 of the 23 erosions seen in phase II, allowing these lesions to be subcategorized as shown in Figures 6–9 with the following histological correlations: in linear erosions, 1

of 12 specimens showed invasive cancer, 2 of 12 showed dysplasia, 4 of 12 showed esophagitis, and 5 of 12 showed normal mucosa; in small, punched-out erosions, 3 of 5 showed dysplasia, 1 of 5 showed esophagitis, and 1 of 5 showed normal mucosa; and in large, broad-based erosions, 2 of 2 showed invasive cancer.

**Table 2.** Correlation of Biopsy Locations With Biopsy Diagnoses

| Biopsy location | n   | Biopsy diagnosis |             |                 |         |           |           |        |           |            |
|-----------------|-----|------------------|-------------|-----------------|---------|-----------|-----------|--------|-----------|------------|
|                 |     | Normal (%)       | Esophagitis |                 |         | Total (%) | Dysplasia |        |           | Cancer (%) |
|                 |     |                  | Mild        | Moderate/severe | Mild    |           | Moderate  | Severe | Total (%) |            |
| Upper 1/3       | 119 | 92 (77)          | 8           | 2               | 10 (8)  | 7         | 4         | 2      | 13 (11)   | 4 (3)      |
| Middle 1/3      | 149 | 110 (74)         | 11          | 5               | 16 (11) | 6         | 1         | 12     | 19 (13)   | 4 (3)      |
| Lower 1/3       | 130 | 112 (86)         | 8           | 4               | 12 (9)  | 2         | 3         | 0      | 5 (4)     | 1 (1)      |
| Total           | 398 | 314 (79)         | 27          | 11              | 38 (10) | 15        | 8         | 14     | 37 (9)    | 9 (2)      |

Plaques and nodules had the highest correlation with squamous dysplasia and cancer of any of our endoscopic categories: 3 of the 16 plaques showed invasive cancer, 11 others showed dysplasia, and the remaining 2 showed normal mucosa; 2 of the 3 nodules showed invasive cancer and the other showed esophagitis.

We found no clear association between any endoscopic appearance and biopsy evidence of esophagitis.

Squamous dysplasia and squamous cancer were strongly associated with the focal visible lesions we categorized as friability, focal red area, erosion, plaque, or nodule. Eight of 15 (53%) of the mild dysplasia specimens, 5 of 8 (63%) of the moderate dysplasia specimens, 11 of 14 (79%) of the severe dysplasia specimens, and 9 of 9 (100%) of the invasive cancer specimens came from these focal target lesions. The sensitivity of these visual categories (combined) for moderately dysplastic or worse mucosa was 25 of 31 (81%), and their combined specificity for such mucosa was 331 of 367 (90%). Analyzed by patient, 4 of 8 patients with mild dysplasia, 2 of 3 patients with moderate dysplasia, 5 of 5 patients with severe dysplasia, and 8 of 8 patients with invasive cancer would have been diagnosed if only a biopsy had been performed in

the areas described visually as friability, focal red area, erosion, plaque, and nodule.

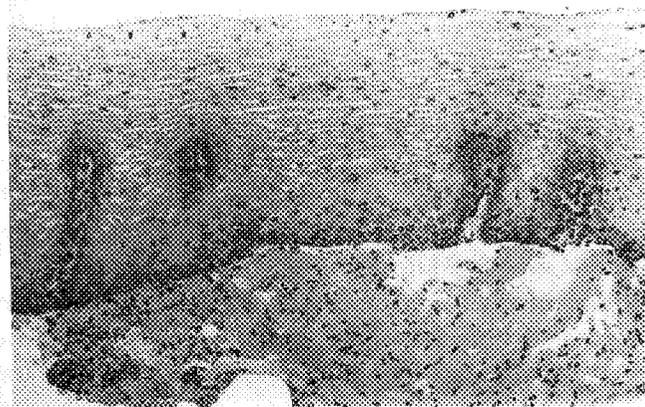
Thirteen dysplastic biopsy specimens were taken from sites other than the visible target lesions described above. However, 8 of these specimens were taken from within 2 cm of a friable area, erosion, or plaque that also showed dysplasia. Only 4 mild dysplasias and 1 moderate dysplasia, all taken from irregular mucosa, were not associated with nearby dysplastic target lesions.

#### Distribution of Histological Findings Within the Esophagus

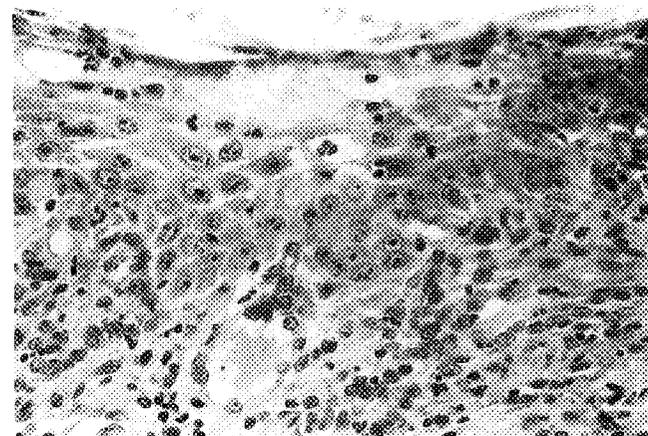
Table 2 shows the biopsy results stratified by location within the esophagus. Esophagitis was fairly evenly distributed, but most of the squamous dysplasia and invasive squamous cancer were found in the middle and upper thirds of the esophagus. Sixteen (70%) of the 23 mucosal sites with specimens showing severe dysplasia or invasive cancer were in the middle third of the esophagus.

#### Discussion

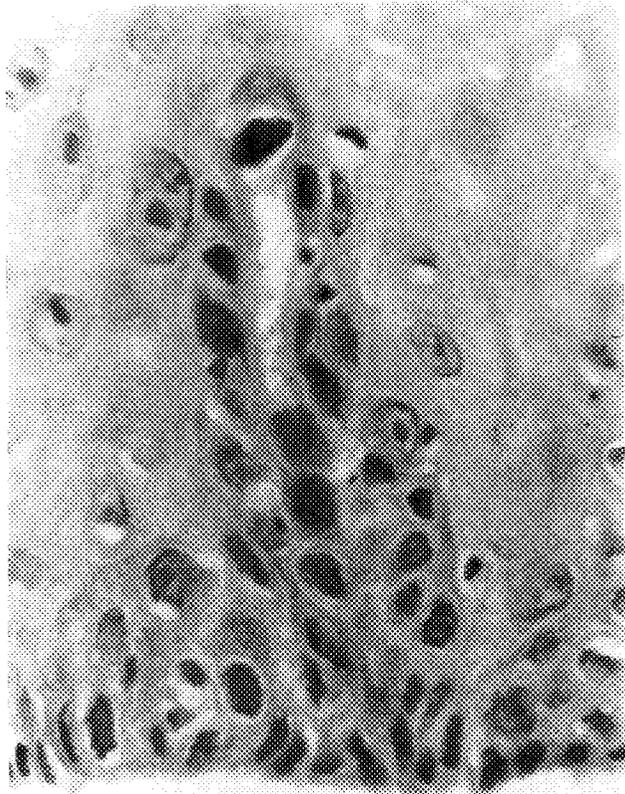
The usefulness of endoscopic biopsies in studying and managing esophageal precursor lesions and



**Figure 12.** Histologically normal esophageal mucosa (H&E, original magnification  $\times 250$ ).

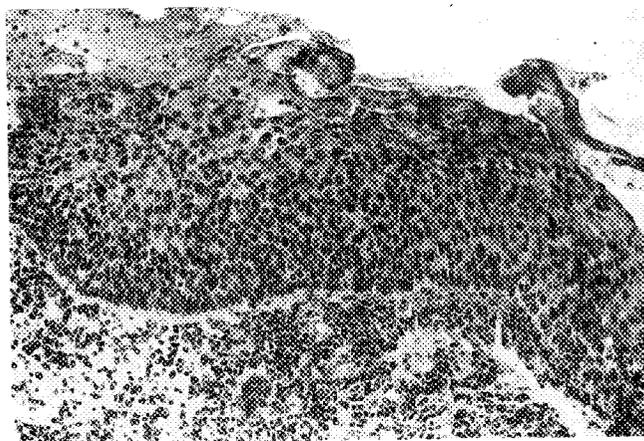


**Figure 13.** Moderate esophagitis. Neutrophils are infiltrating the epithelium (H&E, original magnification  $\times 400$ ).

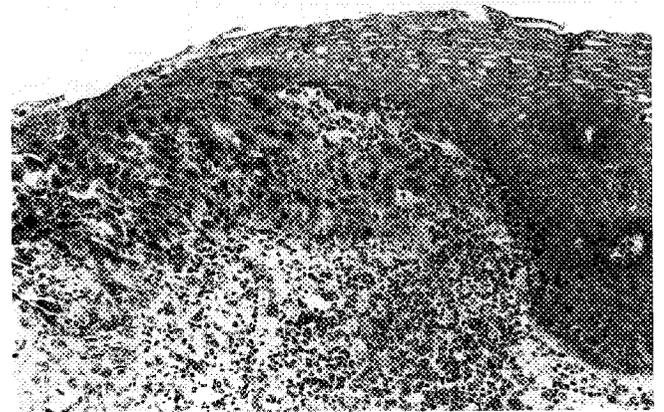


**Figure 14.** Mild squamous dysplasia. Note the atypical cells with large hyperchromatic nuclei. These cells are confined to the basal layers of the epithelium (H&E, original magnification  $\times 400$ ).

early-stage esophageal cancer depends on the ability to reliably identify a patient's worst mucosal disease. Each endoscopic biopsy samples only a small fraction of the esophageal mucosa, so the ability of biopsies to



**Figure 15.** Severe squamous dysplasia. Atypical cells occupy the full thickness of the epithelium with little or no surface maturation (H&E, original magnification  $\times 250$ ).



**Figure 16.** Early invasive squamous cancer. A tongue of malignant epithelial cells (on the left) is invading the lamina propria. Normal squamous epithelium can be seen on the right (H&E, original magnification  $\times 250$ ).

identify focal mucosal abnormalities depends on the visibility of those abnormalities and the number of specimens taken. If focal abnormalities are endoscopically visible, then a few targeted biopsies should be sufficient to diagnose them; if they are invisible, a larger number of systematic biopsy specimens must be taken to identify or exclude them. Examples of such focal and invisible mucosal lesions which often require many biopsies to locate are dysplasia and intramucosal adenocarcinoma arising in Barrett's esophagus.<sup>7</sup>

Our results show that squamous dysplasia and squamous cancer of the esophagus in this population are usually visible as distinct, targetable lesions. If we had limited our protocol to obtaining specimens from the target lesions we called friability, focal red area, erosion, plaque, and nodule, we would have performed biopsies on only 61 of 398 (15%) of the mucosal sites sampled in our full protocol but would have identified 15 of 16 (94%) of the patients with moderate dysplasia or worse diagnoses (including all 8 patients with cancer).

Of note, 8 of the 13 dysplastic specimens that did not come from target lesions came from sites within 2 cm of such lesions. While this may reflect imperfect biopsy site descriptions or localizations during rapid examinations of unanesthetized patients, it may also reflect an extension of dysplasia beyond the visible borders of the target lesions. If the latter is true, *in vivo* mucosal staining or other techniques may be useful to more completely outline the extent of mucosal abnormalities.

Unlike other investigators,<sup>12</sup> we could not correlate

mucosal wrinkling (even the prominent wrinkling in our irregular mucosa category) with histological esophagitis. We wonder if this wrinkled appearance may have been related to the fact that our patients were not anesthetized during the procedure. The separate finding of circumferential ribbing (Figure 3), which was seen in both normal and irregular mucosae, may also have been related to the lack of anesthesia. Such a pattern has been previously described in double-contrast esophagrams and has been attributed to contractions of the muscularis mucosae.<sup>13</sup>

Published opinions vary concerning the visibility of squamous dysplasia and early squamous cancer of the esophagus. In endoscopic surveys, Crespi et al. found that "no specific endoscopic patterns were correlated with the histological finding of dysplasia",<sup>12</sup> whereas Yang and Qiu noted that "the histological diagnosis of dysplasia shows a positive correlation with the severity of chronic esophagitis diagnosed endoscopically."<sup>14</sup> It should be noted that these investigators were primarily examining population prevalences of endoscopic and histological findings and accordingly compared these findings by patient; they did not correlate the mucosal appearances and biopsy diagnoses of individual biopsy sites. It should also be mentioned that computerized image management technology, which greatly improved our ability to accurately record mucosal appearances, was not available in these earlier studies.

Investigators reporting the endoscopic and gross pathological appearances of case series of early esophageal cancer,<sup>15-17</sup> including cases of intraepithelial cancer which we would have classified as severe dysplasia, have described visible surface abnormalities similar to our target lesions of focal red area (called superficial flat,<sup>15</sup> congestive,<sup>16</sup> or occult<sup>17</sup>), erosion (called superficial depressed<sup>15</sup> or erosive<sup>16,17</sup>), plaque (called superficial elevated-plateau type<sup>15</sup> or plaque-like<sup>16,17</sup>), and nodule (called superficial elevated-polypoid type<sup>15</sup> or polypoid<sup>16,17</sup>). As with most case series, these investigators did not report the visual and histological findings of systematically sampled noncancerous mucosa and therefore could not evaluate the sensitivity or specificity of their target lesions for dysplasia or cancer as we have done.

In the present study, only 24 of 63 (38%) subjects with balloon cytology diagnoses of squamous dysplasia or cancer had endoscopic biopsies showing these lesions. Several factors may have contributed to this discrepancy, including regression of some of the dysplastic lesions in the time between the cytological and endoscopic examinations (a 2-6-year interval for the

phase I subjects), insufficient sampling by endoscopic biopsies, and false positive cytological diagnoses. Insufficient biopsy sampling of the mucosa was probably not a major factor in this study, because only 5 (2%) of the 295 specimens from mucosa without focal endoscopic lesions showed moderate or severe dysplasia and none contained invasive cancer (Table 1). With regard to the cytological diagnoses, it should be noted that these findings were not subjected to consensus review for accuracy and uniformity. Longitudinal follow-up studies are needed to help clarify discrepancies between balloon cytology and endoscopic biopsy findings.

Our findings do not address several issues. One is that balloon cytology-negative patients might have smaller, more difficult to visualize dysplastic or carcinomatous lesions that might be missed at endoscopy and on biopsy. A second is whether the endoscopy-biopsy correlations in this study apply to lower-risk populations such as those in North America and in Europe.

We suggest the following provisional guidelines for endoscopic surveys of the esophageal mucosa in high-risk squamous cancer areas, both for research studies and for clinical management: (1) Biopsy specimens should be obtained from all plaque, nodule, erosion, and friable areas. (2) Normal areas (including mildly wrinkled mucosa in the unanesthetized patient) and isolated small white patches need not be sampled. (3) Biopsy specimens should be obtained from diffusely irregular (prominently wrinkled) mucosa and distinct areas of focal reddening at the endoscopist's discretion.

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