

Effect of Segment Length on Risk for Neoplastic Progression in Patients with Barrett Esophagus

Rebecca E. Rudolph, MD, MPH; Thomas L. Vaughan, MD, MPH; Barry E. Storer, PhD; Rodger C. Haggitt, MD; Peter S. Rabinovitch, MD, PhD; Douglas S. Levine, MD; and Brian J. Reid, MD, PhD

Background: The increased risk for esophageal adenocarcinoma associated with long-segment (≥ 3 cm) Barrett esophagus is well recognized. Recent studies suggest that short-segment (< 3 cm) Barrett esophagus is substantially more common; however, the risk for neoplastic progression in patients with this disorder is largely unknown.

Objective: To examine the relation between segment length and risk for aneuploidy and esophageal adenocarcinoma in patients with Barrett esophagus.

Design: Prospective cohort study.

Setting: University medical center in Seattle, Washington.

Patients: 309 patients with Barrett esophagus.

Measurements: Patients were monitored for progression to aneuploidy and adenocarcinoma by repeated endoscopy with biopsy for an average of 3.8 years. Cox proportional hazards analysis was used to calculate adjusted relative risks and 95% CIs.

Results: After adjustment for histologic diagnosis at study entry, segment length was not related to risk for cancer in the full cohort ($P > 0.2$ for trend). When patients with high-grade dysplasia at baseline were excluded, however, a nonsignificant trend was observed; based on a linear model, a 5-cm difference in segment length was associated with a 1.7-fold (95% CI, 0.8-fold to 3.8-fold) increase in cancer risk. Among all eligible patients, a 5-cm difference in segment length was associated with a small increase in the risk for aneuploidy (relative risk, 1.4 [CI, 1.0 to 2.1]; $P = 0.06$ for trend). A similar trend was observed among patients without high-grade dysplasia at baseline.

Conclusions: The risk for esophageal adenocarcinoma in patients with short-segment Barrett esophagus was not substantially lower than that in patients with longer segments. Although our results suggest a small increase in risk for neoplastic progression with increasing segment length, additional follow-up is needed to determine whether the patterns of risk occurred by chance or represent true differences. Until more data are available, the frequency of endoscopic surveillance should be selected without regard to segment length.

In Barrett esophagus, the normal stratified squamous epithelium of the esophagus is replaced by specialized columnar epithelium in response to the tissue injury caused by chronic gastroesophageal reflux (1). Barrett esophagus is present in approximately 5% to 15% of persons with clinical indications for elective upper endoscopy (2–5). The results of several recent studies suggest that most patients with Barrett esophagus have short-segment (< 3 cm) Barrett esophagus (2–7).

Patients with long-segment (≥ 3 cm) Barrett esophagus are known to have a much greater risk for esophageal adenocarcinoma than members of the general population (8–11). Because investigators were initially uncertain whether short-segment Barrett esophagus predisposed persons to esophageal adenocarcinoma and because short-segment Barrett esophagus is more difficult to diagnose endoscopically (12), patients with short segments were often excluded from studies of the natural history of Barrett esophagus (8–11, 13, 14). Since the late 1980s, however, there have been several reports of esophageal adenocarcinoma in patients with short-segment Barrett esophagus (5, 15–18). Although this suggests that patients with short-segment Barrett esophagus are at increased risk for esophageal adenocarcinoma, the extent of the increase is largely unknown.

The survival of patients who receive a diagnosis of esophageal adenocarcinoma is usually poor. More than 90% of patients with invasive disease die within 5 years of diagnosis (19). If tumors are resected at an early stage, however, survival improves substantially (20–22). Therefore, many authors have recommended regular endoscopic surveillance for patients with Barrett esophagus who are good surgical candidates (20, 21, 23–27) and prompt resection of the entire Barrett segment if cancer is identified (22, 28, 29). However, endoscopic surveillance has several disadvantages, including its high cost, procedure-related risks, inconvenience, and discomfort (30, 31). Because only a small percentage of patients with Barrett esophagus will develop cancer, it is reasonable to question the merits of frequent endoscopic surveillance for all such persons (11, 12, 23).

We hypothesized that the risk for esophageal adenocarcinoma would increase with Barrett segment length. If this was true, it might be appropriate to perform endoscopic surveillance less frequently in

Ann Intern Med. 2000;132:612-620.

For author affiliations, current addresses, and contributions, see end of text.

patients with short-segment Barrett esophagus than in those with longer segments. To investigate this hypothesis, we conducted a prospective cohort study among patients who were participating in the Seattle Barrett's Esophagus Project, which includes regular endoscopic surveillance. We determined the incidence of esophageal adenocarcinoma in patients with short-segment Barrett esophagus and examined the relation between segment length and cancer risk through multivariate analyses. We also examined the relation between segment length and aneuploidy, a genetic abnormality that usually precedes the development of esophageal adenocarcinoma and has been shown to predict progression to cancer (32). Aneuploidy was chosen as an outcome of interest primarily because it occurred more frequently than cancer in the study cohort, thus increasing statistical power for analyzing the relation between segment length and neoplastic progression.

Methods

Study Sample

Study participants were selected from a cohort of patients who were enrolled in the Seattle Barrett's Esophagus Project and underwent endoscopic surveillance between July 1983 and July 1998. Gastroenterologists who practice in Washington State have been the primary source of referrals to this cohort. All cohort members who met the following criteria as of 10 July 1998 were included in our study: 1) at least two endoscopies with histologic diagnoses, 2) presence of specialized columnar epithelium in the esophagus at the first endoscopy, 3) a record of Barrett segment length at the first endoscopy, 4) no esophageal cancer at the first endoscopy, and 5) no history of esophageal cancer. Three hundred nine persons qualified for the study. All of the study patients received counseling on lifestyle measures to reduce gastroesophageal reflux, and most used acid-reducing medication regularly. The Human Subjects Review Committee at the University of Washington approved the study.

To evaluate the relation between segment length and aneuploidy, it was necessary to have information about the presence or absence of aneuploidy from at least two endoscopies. Of the 208 patients for whom this information was available, 37 had aneuploidy at the first qualifying endoscopy and were therefore excluded, leaving 171 for analyses with the aneuploidy end point.

Endoscopy

Barrett segment length was defined as the distance between the esophagogastric junction and the

squamocolumnar junction. The esophagogastric junction was defined as the endoscopic lower esophageal sphincter or, if this was not apparent, the location at which the tubular esophagus joined the proximal margin of the gastric folds. The squamocolumnar junction was defined as the location at which the light-pink mucosa of the squamous-lined esophagus joined the red mucosa of the columnar-lined esophagus. The locations of these landmarks were determined as the endoscope was withdrawn from the stomach to the upper esophagus. Air was always removed from the stomach before this assessment.

Tissue samples were obtained by using the "turn and suction" technique and jumbo biopsy forceps, as described elsewhere (33, 34). Until 1992, four biopsies (one per quadrant of the esophagus) were obtained from every other centimeter of the Barrett segment in all patients. From 1992 through 1998, four biopsies (one per quadrant of the esophagus) were obtained from every centimeter of the Barrett segment in patients with a history of high-grade dysplasia. In all patients, at least one control biopsy specimen was also taken from the gastric fundus and several biopsy specimens were taken from any visible mucosal abnormality.

Each biopsy specimen was oriented on plastic mesh, epithelial surface upward, as soon as it was obtained. The gastric biopsy specimen and half of the first biopsy specimen from every level were placed in separate vials containing minimum essential medium with 5% serum and 10% dimethyl sulfoxide. The specimens were then immediately placed on wet ice and were stored at -70°C for subsequent flow cytometric analysis. The other half of the first biopsy specimen and the remaining three biopsy specimens from each level were placed in Hollande solution (one vial per level) for subsequent histologic examination.

The most advanced histologic diagnosis at a given endoscopy was used to select the follow-up interval to the next endoscopy and the biopsy protocol for that endoscopy. The median interval between endoscopies was 25 months for patients with a baseline diagnosis of metaplasia, 18 months for patients with a baseline diagnosis of indefinite for dysplasia or low-grade dysplasia, and 5 months for patients with a baseline diagnosis of high-grade dysplasia.

Histologic Examination

The fixed biopsy specimens were serially cut into 4- μm sections, mounted onto slides, and stained with hematoxylin and eosin alone or with hematoxylin and eosin, saffron, and Alcian blue at a pH of 2.5. The slides were examined by an experienced gastrointestinal pathologist, as described elsewhere (35). A histologic diagnosis of negative for dysplasia, indefinite for dysplasia, low-grade dysplasia, high-

grade dysplasia, or intramucosal carcinoma was assigned to each slide by using established criteria (36). Because pathologists cannot consistently differentiate between the diagnoses of indefinite for dysplasia and low-grade dysplasia (36), these histologic diagnoses were combined into one category for all statistical analyses.

DNA Content Flow Cytometry

The methods used to prepare biopsy specimens for cell sorting, to perform flow cytometry, and to analyze the resulting data have been described elsewhere (34). Aneuploidy was diagnosed if, in at least one biopsy specimen from a particular endoscopy, two discrete peaks were observed on the histogram (one reflecting the presence of an aneuploid population and the other reflecting the presence of a diploid population) and the aneuploid peak represented at least 2.5% of the cells in the biopsy specimen (32). Tetraploid DNA contents in the range of 3.85N to 4.1N were also excluded.

Demographic, Lifestyle, and Anthropometric Data

Trained staff used a standard questionnaire to interview 71% (220 of 309) of the patients in this study in person between January 1995 and July 1998. Collected data included information on cigarette use, usual weight, height, ethnicity, annual income, education, and symptoms of gastroesophageal reflux. Information on age at study entry and sex was extracted from electronic patient records.

Statistical Analysis

Incidence rates were calculated by dividing the total number of cases by the total follow-up time (in person-years) in the full study sample or in defined subsets of the study sample. For each patient, follow-up time within the cohort began on the date of the first endoscopy that met the eligibility criteria. In analyses in which cancer was the outcome of interest, follow-up time ended on the date of the last endoscopy before the end of our study (10 July 1998) or on the date of the endoscopy that led to a diagnosis of cancer, whichever occurred first. Similarly, in analyses in which aneuploidy was the outcome of interest, follow-up time ended on the date of the last endoscopy before the end of the study or on the date of the endoscopy that led to a diagnosis of aneuploidy. In the analyses in which aneuploidy was the disease end point, a small number of participants ($n = 10$) received a diagnosis of cancer at an endoscopy for which no flow cytometry data were available. Because approximately 90% of esophageal adenocarcinomas contain aneuploid cell populations (27), a diagnosis of cancer was considered to be a diagnosis of aneuploidy in these cases.

Cox proportional hazards models were used to

estimate relative risks and 95% CIs for the effect of Barrett segment length at study entry on the risk for progression to cancer or aneuploidy. Barrett segment length was introduced into the Cox models as a continuous variable (measured in whole centimeters) or as a set of dummy variables (<3 cm, 3 to 6 cm, 7 to 10 cm, and >10 cm). Variables evaluated as potential confounders were histologic diagnosis at study entry (metaplasia, indefinite for dysplasia or low-grade dysplasia, high-grade dysplasia), age at study entry (in years), sex, cigarette use (ever, never), ethnicity (white, African American, Asian, Native American, other), annual income (<\$15 000, \$15 000 to \$30 000, \$30 000 to \$45 000, >\$45 000), education (<9th grade, 9th through 12th grade, vocational training, some college), duration of heartburn (in years), duration of acid regurgitation (in years), and usual body mass index.

We calculated body mass index as weight in kilograms divided by height in meters squared and categorized it into quartiles by using the sex-specific distributions of usual body mass index among controls in the study by Chow and colleagues (37). Information on cigarette use, ethnicity, annual income, education, symptoms of gastroesophageal reflux, and usual body mass index was available for approximately 70% of patients. The potential confounding effects of each of these variables were assessed only among patients for whom complete data were available. Only histologic diagnosis at study entry was observed to be a confounder and was therefore retained in all of the final models.

The statistical significance of any trend in the relative risk estimates for segment length was determined by performing a likelihood ratio test comparing models with and without segment length entered as a continuous variable. To examine whether the effect of segment length on the risk for neoplastic progression varied with baseline histologic diagnosis, separate relative risk estimates were generated for each category of this variable. All analyses were conducted by using Stata statistical software, version 5.0 (Stata Corp., College Station, Texas) (38).

Role of the Funding Source

The National Cancer Institute funded this study but had no role in the collection, analysis, or interpretation of the data or in the decision to submit the paper for publication.

Results

The 309 patients were followed for a mean (\pm SD) of 3.8 ± 3.4 years. The mean segment length at study entry was 5.6 ± 4.0 cm. Patients with short-segment Barrett esophagus were younger and were

Table 1. Characteristics of the Cohort at Study Entry

| Characteristic | Patients with Short-Segment Barrett Esophagus (<3 cm) | Patients with Long-Segment Barrett Esophagus (≥3 cm) | All Patients |
|---|---|--|--------------|
| | ← n (%) → | | |
| Histologic diagnosis | | | |
| Metaplasia | 41 (49.4) | 80 (35.4) | 121 (39.2) |
| Indefinite for dysplasia or low-grade dysplasia | 28 (33.7) | 86 (38.0) | 114 (36.9) |
| High-grade dysplasia | 14 (16.9) | 60 (26.6) | 74 (24.0) |
| Age* | | | |
| <40 y | 3 (3.6) | 12 (5.3) | 15 (4.8) |
| 40–49 y | 20 (24.1) | 29 (12.8) | 49 (15.9) |
| 50–59 y | 19 (22.9) | 54 (23.9) | 73 (23.6) |
| 60–69 y | 25 (30.1) | 72 (31.9) | 97 (31.4) |
| ≥70 y | 16 (19.3) | 59 (26.1) | 75 (24.3) |
| Sex | | | |
| Male | 67 (80.7) | 185 (81.9) | 252 (81.6) |
| Female | 16 (19.3) | 41 (18.1) | 57 (18.4) |

* Mean age was 58 years for patients with short-segment Barrett esophagus, 61 years for patients with long-segment Barrett esophagus, and 60 years for all patients.

less likely to have high-grade dysplasia at study entry than those with long-segment Barrett esophagus (Table 1). The ratio of men to women was approximately 4 in both groups. The distributions of histologic diagnoses, age, and sex among the interviewed patients were similar to those in the study sample as a whole. Nearly all of the interviewed patients (98.6%) reported a history of heartburn or acid regurgitation. The mean duration of heartburn and acid regurgitation among the interviewed patients was 21.9 years and 14.5 years, respectively; duration did not vary significantly with segment length. As a group, the interviewed patients were primarily white, high-income, well-educated, and overweight (Table 2). Patients with short-segment Barrett esophagus more often currently smoked or had ever smoked and had fewer years of education than those with longer segments. None of the observed differences between patients with short-segment Barrett esophagus and those with long-segment Barrett esophagus were statistically significant by the Pearson chi-square test ($P > 0.05$).

Cancer End Point

In the full cohort of 309 patients, the incidence of cancer was somewhat greater among those with longer segments (Table 3). The same trend was observed among patients with a baseline diagnosis of metaplasia or indefinite for dysplasia/low-grade dysplasia but not among those with a baseline diagnosis of high-grade dysplasia. Because similar results were observed for patients with metaplasia and those with diagnoses of indefinite for dysplasia or low-grade dysplasia at baseline, we combined the data from these patients in Table 3. After adjustment for histologic diagnosis at study entry, segment

length did not affect the risk for progression to cancer in the study sample as a whole (Table 3). Among patients without high-grade dysplasia at study entry, however, we observed a nonsignificant trend toward an increased cancer risk in those with longer segments. No association between segment length and cancer risk was observed among patients with high-grade dysplasia at study entry. The relation between segment length and cancer risk was essentially the same when segment length was entered into the Cox models as a continuous variable. For example, a 5-cm difference in segment length was associated with a 1.7-fold (95% CI, 0.8-fold to 3.8-fold) increase in cancer risk in patients without high-grade dysplasia at baseline but was not associated with an increase in cancer risk among patients with high-grade dysplasia at baseline (relative risk, 1.1 [CI, 0.7 to 1.8]).

Because esophageal adenocarcinoma diagnosed in the first 3 months of the study could be prevalent rather than incident, we repeated our analyses after excluding the 7 patients whose adenocarcinoma was detected during this period. The exclusion of these 7 persons, all of whom had high-grade dysplasia at

Table 2. Characteristics of Interviewed Patients

| Characteristic | Patients with Short-Segment Barrett Esophagus (<3 cm) | Patients with Long-Segment Barrett Esophagus (≥3 cm) | All Patients |
|---------------------------|---|--|--------------|
| | ← n (%) → | | |
| Cigarette use | | | |
| Current | 13 (20.0) | 14 (9.0) | 27 (12.3) |
| Former | 37 (56.9) | 91 (58.7) | 128 (58.2) |
| Never | 15 (23.1) | 50 (32.3) | 65 (29.6) |
| Ethnicity | | | |
| White | 63 (96.9) | 148 (95.5) | 211 (95.9) |
| African American | 0 (0) | 0 (0) | 0 (0) |
| Asian | 1 (1.5) | 1 (0.6) | 2 (0.9) |
| Native American | 0 (0) | 2 (1.3) | 2 (0.9) |
| Other | 0 (0) | 4 (2.6) | 4 (1.8) |
| Declined to answer | 1 (1.5) | 0 (0) | 1 (0.4) |
| Annual income | | | |
| <\$15 000 | 7 (10.8) | 10 (6.4) | 17 (7.7) |
| \$15 000–\$30 000 | 11 (16.9) | 45 (29.0) | 56 (25.4) |
| \$30 000–\$45 000 | 12 (18.5) | 38 (24.5) | 50 (22.7) |
| \$45 000–\$60 000 | 8 (12.3) | 20 (12.9) | 28 (12.7) |
| >\$60 000 | 21 (32.3) | 38 (24.5) | 59 (26.8) |
| Declined to answer | 6 (9.2) | 3 (1.9) | 9 (4.1) |
| Did not know | 0 (0) | 1 (0.6) | 1 (0.4) |
| Education | | | |
| <9th grade | 1 (1.6) | 3 (1.9) | 4 (1.8) |
| 9th–12th grade | 26 (40.6) | 39 (25.2) | 65 (29.7) |
| Vocational training | 2 (3.1) | 10 (6.4) | 12 (5.5) |
| Some college | 35 (54.7) | 103 (66.4) | 138 (63.0) |
| Information missing | 1 (1.5) | 0 (0) | 1 (0.4) |
| Usual body mass index* | | | |
| First quartile (lowest) | 5 (7.7) | 11 (7.1) | 16 (7.3) |
| Second quartile | 11 (16.9) | 33 (21.3) | 44 (20.0) |
| Third quartile | 19 (29.2) | 42 (27.1) | 61 (27.7) |
| Fourth quartile (highest) | 30 (46.2) | 69 (44.5) | 99 (45.0) |

* Quartiles are based on sex-specific distributions of usual body mass index among controls in the study by Chow and colleagues (37); first quartile, <23.12 kg/m² (men) and <21.95 kg/m² (women); second quartile, 23.12–25.08 kg/m² (men) and 21.95–24.12 kg/m² (women); third quartile, 25.09–27.31 kg/m² (men) and 24.13–27.43 kg/m² (women); fourth quartile, ≥27.32 kg/m² (men) and ≥27.44 kg/m² (women).

Table 3. Barrett Segment Length and the Risk for Progression to Esophageal Adenocarcinoma according to Histologic Diagnosis at Study Entry

| Segment Length | Patients Follow-up | | Patients in Whom Cancer Was Detected | Incidence* | Relative Risk (95% CI) |
|------------------------------|--------------------|--------------|--------------------------------------|------------|------------------------|
| | n | person-years | | | |
| All histologic diagnoses†‡§ | | | | | |
| <3 cm | 83 | 279.8 | 7 | 2.5 | 1.0 (referent) |
| 3–6 cm | 108 | 386.2 | 11 | 2.8 | 0.8 (0.3–2.2) |
| 7–10 cm | 82 | 376.8 | 12 | 3.2 | 1.0 (0.4–2.5) |
| >10 cm | 36 | 141.7 | 10 | 7.0 | 1.2 (0.4–3.1) |
| All lengths | 309 | 1184.5 | 40 | 3.4 | |
| High-grade dysplasia absent§ | | | | | |
| <3 cm | 69 | 256.9 | 1 | 0.4 | 1.0 (referent) |
| 3–6 cm | 84 | 342.6 | 2 | 0.6 | 1.5 (0.1–16) |
| 7–10 cm | 62 | 336.9 | 3 | 0.9 | 1.8 (0.2–18) |
| >10 cm | 20 | 108.7 | 2 | 1.8 | 3.7 (0.3–45) |
| All lengths | 235 | 1045.1 | 8 | 0.8 | |
| High-grade dysplasia present | | | | | |
| <3 cm | 14 | 22.9 | 6 | 26.2 | 1.0 (referent) |
| 3–6 cm | 24 | 43.6 | 9 | 20.7 | 0.8 (0.3–2.3) |
| 7–10 cm | 20 | 39.9 | 9 | 22.6 | 0.8 (0.3–2.4) |
| >10 cm | 16 | 32.9 | 8 | 24.3 | 0.9 (0.3–2.8) |
| All lengths | 74 | 139.3 | 32 | 23.0 | |

* Number of persons per 100 person-years who received a diagnosis of cancer.
 † Metaplasia, indefinite for dysplasia, low-grade dysplasia, and high-grade dysplasia.
 ‡ Relative risk estimates adjusted for histologic diagnosis (metaplasia, indefinite for dysplasia or low-grade dysplasia, high-grade dysplasia) at study entry.
 § $P > 0.2$ for trend.
 || Relative risk estimates adjusted for histologic diagnosis (metaplasia, indefinite for dysplasia or low-grade dysplasia) at study entry.

the first endoscopy, did not materially alter the estimates for the effect of segment length on the risk for progression to cancer. For example, the relative risk comparing persons with a segment length greater than 10 cm to those with a segment length less than 3 cm changed from 1.2 (CI, 0.4 to 3.1) to 1.4 (CI, 0.5 to 4.4). Similar results were observed when the 11 patients who received a diagnosis of esophageal adenocarcinoma during the first 6 months of follow-up were excluded. All of these 11 patients had high-grade dysplasia at baseline.

Of the 83 patients with a Barrett segment less than 3 cm at study entry, 7 had specialized intestinal metaplasia in the distal esophagus but no visible columnar epithelium above the esophagogastric junction and were therefore assigned a segment length of 0 cm. All of the patients who lacked visible columnar epithelium in the esophagus had symptoms of gastroesophageal reflux disease and most (6 of 7) had a hiatal hernia. The clinical indications for biopsy in these patients were a history of known ($n = 4$) or suspected ($n = 3$) Barrett esophagus based on referring endoscopic evaluations or frequent symptoms related to gastroesophageal reflux; in most (6 of 7), biopsies obtained from the endoscopic squamocolumnar junction showed specialized intestinal metaplasia directly adjacent to esophageal squamous epithelium. None of these 7 patients de-

veloped cancer during 23.1 person-years of follow-up. The cancer incidence rates and relative risk estimates were essentially the same when the patients who lacked visible columnar epithelium in the esophagus at baseline were excluded from our analyses. For example, the relative risk comparing persons with a segment length greater than 10 cm to those with a segment length less than 3 cm changed from 1.2 (CI, 0.4 to 3.1) to 1.1 (CI, 0.4 to 3.0).

Surgical resection of the Barrett segment was performed on 11 patients with a preoperative diagnosis of high-grade dysplasia. The indications for surgery included persistent, endoscopically visible mucosal abnormalities; difficulty discerning whether invasion into the lamina propria had occurred; and patient preference. To examine the extent to which the censoring of these patients may have affected our results, we repeated our analyses after assigning a diagnosis of cancer to all 11 persons with the surgery date as the date of diagnosis. No changes were observed in the risk estimates for the effect of segment length on cancer risk in the cohort as a whole or in the subset of patients with high-grade dysplasia at study entry. Among patients without high-grade dysplasia at baseline, however, the risk

Table 4. Barrett Segment Length and the Risk for Progression to Aneuploidy according to Histologic Diagnosis at Baseline*

| Segment Length | Patients Follow-up | | Patients in Whom Aneuploidy Was Detected | Incidence† | Relative Risk (95% CI) |
|--------------------------------|--------------------|--------------|--|------------|------------------------|
| | n | person-years | | | |
| All histologic diagnoses‡§ | | | | | |
| <3 cm | 46 | 179.8 | 10 | 5.6 | 1.0 (referent) |
| 3–6 cm | 55 | 219.2 | 11 | 5.0 | 1.0 (0.4–2.4) |
| 7–10 cm | 57 | 224.5 | 19 | 8.5 | 1.5 (0.7–3.3) |
| >10 cm | 13 | 56.4 | 8 | 14.2 | 2.2 (0.8–5.8) |
| All lengths | 171 | 679.9 | 48 | 7.0 | |
| High-grade dysplasia absent¶** | | | | | |
| <3 cm | 37 | 167.6 | 3 | 1.8 | 1.0 (referent) |
| 3–6 cm | 47 | 208.9 | 6 | 2.9 | 1.4 (0.4–5.8) |
| 7–10 cm | 46 | 212.9 | 11 | 5.2 | 2.2 (0.6–8.0) |
| >10 cm | 8 | 53.1 | 4 | 7.5 | 2.4 (0.5–12) |
| All lengths | 138 | 642.5 | 24 | 3.7 | |
| High-grade dysplasia present†† | | | | | |
| <3 cm | 9 | 12.3 | 7 | 57.0 | 1.0 (referent) |
| 3–6 cm | 8 | 10.3 | 5 | 48.6 | 0.8 (0.2–2.6) |
| 7–10 cm | 11 | 11.6 | 8 | 68.8 | 1.1 (0.4–3.3) |
| >10 cm | 5 | 3.4 | 4 | 118.6 | 1.9 (0.5–6.9) |
| All lengths | 33 | 37.6 | 24 | 63.9 | |

* If cancer was detected before aneuploidy, a diagnosis of cancer was counted as a diagnosis of aneuploidy.
 † Number of persons per 100 person-years who received a diagnosis of aneuploidy.
 ‡ Metaplasia, indefinite for dysplasia, low-grade dysplasia, and high-grade dysplasia.
 § Relative risk estimates adjusted for histologic diagnosis (metaplasia, indefinite for dysplasia or low-grade dysplasia, high-grade dysplasia) at baseline.
 || $P = 0.06$ for trend.
 ¶ $P = 0.2$ for trend.
 ** Relative risk estimates adjusted for histologic diagnosis (metaplasia, indefinite for dysplasia or low-grade dysplasia) at baseline.
 †† $P > 0.2$ for trend.

estimates decreased somewhat. Whereas a 5-cm difference in segment length was associated with a 1.7-fold increase in the risk for esophageal adenocarcinoma in the main analysis, the same length difference was associated with a 1.4-fold increase in cancer risk in this sensitivity analysis.

Aneuploidy End Point

The 171 patients who met the eligibility criteria for the aneuploidy end point analyses were followed for a mean of 4.0 ± 3.3 years. The mean segment length at baseline was 5.4 ± 3.5 cm. The percentage of persons with high-grade dysplasia in this group was somewhat lower than in the full cohort (19% compared with 24%) and did not vary across the two categories of segment length. The distributions of age and sex among patients who qualified for the aneuploidy end point analyses were similar to those in the full cohort. In addition, the distributions of cigarette smoking, ethnicity, annual income, education, and usual body mass index among the interviewed patients who were eligible for these analyses were similar to the patterns observed in the interviewed patients from the full cohort.

The incidence of aneuploidy tended to be greater among patients with longer segments (**Table 4**). This trend was also observed among patients with a baseline diagnosis of metaplasia or indefinite for dysplasia/low-grade dysplasia but was weaker among those with high-grade dysplasia. After adjustment for histologic diagnosis at baseline, we observed a nonsignificant trend toward an increased risk for aneuploidy among patients with longer segments, regardless of the way segment length was modeled. With the linear model, a 5-cm difference in segment length was associated with a 1.4-fold (CI, 1.0 to 2.1) difference in the risk for aneuploidy ($P = 0.06$ for trend). A similar trend was observed among patients without high-grade dysplasia at baseline. The exclusion of patients who received a diagnosis of aneuploidy during the first 3 or 6 months of follow-up did not materially alter the risk estimates.

Discussion

The results of this prospective cohort study suggest that the risk for esophageal adenocarcinoma in patients with short-segment Barrett esophagus is not substantially lower than that in patients with longer segments. In our multivariate analyses, we adjusted for histologic diagnosis at baseline so that we could determine whether segment length provided any additional information on the likelihood that a person with Barrett esophagus would develop esophageal adenocarcinoma. After adjusting for this variable, we did not observe an association between segment

length and the risk for esophageal adenocarcinoma in the full cohort of 309 patients. When patients with high-grade dysplasia were excluded, however, we observed a nonsignificant trend toward increased risk for cancer among patients with longer segments. Greater segment length was also associated with a nonsignificant, moderate increase in the risk for aneuploidy.

Although several investigators have detected esophageal adenocarcinoma in patients with short-segment Barrett esophagus (5, 15–18), the precise incidence of adenocarcinoma in this group is unknown. To date, only two prospective cohort studies of patients with short segments have been published. Sharma and coworkers (18) detected esophageal adenocarcinoma in 1 of 32 patients with short-segment Barrett esophagus during an average follow-up of 3 years. Weston and colleagues (39) did not detect esophageal adenocarcinoma in any of 26 study participants with a segment length of less than 2 cm who were followed for an average of 1.6 years. If the data from the two studies are combined, the incidence of esophageal adenocarcinoma among patients who had short-segment Barrett esophagus without high-grade dysplasia was 0.7 per 100 person-years, which is similar to our result of 0.4 per 100 person-years. Clearly, these incidence rates are based on relatively short periods of follow-up and should be interpreted with caution.

Few investigators have studied the relation between Barrett segment length and the risk for esophageal adenocarcinoma in patients with longer segments (≥ 3 cm) (9–11, 13, 14, 28, 40). Risk estimates are available from only one study. Menke-Pluymers and coworkers (14) conducted a hospital-based retrospective case-control study of 96 patients with columnar-lined esophagus and 62 patients with esophageal adenocarcinoma in columnar-lined esophagus. The authors did not specify whether the columnar epithelium was specialized intestinal metaplasia or whether dysplasia was present. Patients with short-segment Barrett esophagus were excluded from the study. After adjustment for age, sex, alcohol use, and smoking, a doubling of segment length was associated with a 1.7-fold increase in the risk for esophageal adenocarcinoma, similar to what we observed in patients without high-grade dysplasia.

Iftikhar and colleagues (13) followed 102 patients with a columnar-lined segment at least 5 cm long for an average of 4.5 years. All patients found to have dysplasia ($n = 10$) or cancer ($n = 4$) during follow-up had a segment length of 8 cm or more at the time of diagnosis. In a retrospective cohort study of 155 patients with a columnar-lined segment at least 3 cm in length, van der Burgh and colleagues (11) diagnosed 8 cases of cancer during the total follow-up period of 1440 person-years. Most of

these cases occurred in patients with a segment length of 10 cm or more. Finally, Harle and coworkers (28) observed that “extended” columnar-lined esophagus (as defined by Ransom and colleagues [41]) was more prevalent in patients with esophageal adenocarcinoma than in those with benign columnar-lined esophagus.

We hypothesized that greater segment length would be a risk factor for neoplastic progression early in carcinogenesis. Even before dysplasia develops, increased rates of cellular proliferation are observed throughout the Barrett segment (1, 42, 43). Although mutagens can damage the DNA of any cell, genetic changes are more likely to result in progression to cancer if the affected cells are proliferating than if they are quiescent (44–46). Therefore, we predicted that patients with longer segments (and consequently more proliferating cells) would have a greater risk for cancer than those with shorter segments. However, because high-grade dysplasia and aneuploidy are strong risk factors for esophageal adenocarcinoma (9, 32, 47), we expected that the effect of segment length on cancer risk would be less evident among patients with one of these abnormalities than among patients with neither abnormality.

Our results support this reasoning because the associations between segment length and risk for aneuploidy or cancer were stronger among patients without high-grade dysplasia at baseline than in those with high-grade dysplasia, and the association with segment length was stronger when aneuploidy was the disease end point. Nevertheless, the observed trends could reasonably have occurred by chance, suggesting that segment length may have no effect on risk for progression or that a small effect is overwhelmed by other, more important risk factors. When our findings are interpreted, the imprecision of our risk estimates (as evidenced by the wide 95% CIs) should also be noted. Because the rate of progression to cancer is slow, particularly in patients without high-grade dysplasia, longer periods of follow-up will be needed to improve their precision.

We used aneuploidy as an intermediate end point in some analyses for two reasons. The first was to increase the statistical power of the study by taking advantage of the fact that the incidence of aneuploidy in our cohort was approximately twice that of cancer. The second was to focus analyses on an outcome that usually precedes cancer and for which we hypothesized that segment length might play a larger etiologic role. Although good evidence suggests that aneuploidy is a valid intermediate marker of esophageal adenocarcinoma (32), the approach also has limitations. In particular, an unknown portion of aneuploid cell populations will manifest as increased 4N cell populations. Because

patients with this type of DNA content abnormality would not have been assigned a diagnosis of aneuploidy in our study, they would have been misclassified with regard to disease outcome. In addition, because flow cytometry data were not available for some follow-up endoscopies, it was necessary to use the diagnosis of esophageal adenocarcinoma as a surrogate for the diagnosis of aneuploidy in 10 patients. However, because aneuploid cell populations are observed in most esophageal adenocarcinomas (27), this is unlikely to have substantially biased our estimates of incidence or relative risk.

Two other limitations of this study should be mentioned. First, when segment length is assessed endoscopically, measurement error is unavoidable (12, 48). The location of the esophagogastric junction frequently changes as a result of respiration, peristalsis, gastric or esophageal distention, or momentary herniation of gastric folds into the esophagus (12). Because the error in measuring segment length is not related to the subsequent risk for disease, its likely effect would be to attenuate the relative risk estimates. Second, information on several potential confounders (cigarette use, ethnicity, annual income, education, symptoms of gastroesophageal reflux, and usual body mass index) was available for only approximately 70% of the study patients. Within this subset of the study sample, however, none of the variables was observed to be a confounder.

A major goal of our study was to determine whether patients with short-segment Barrett esophagus are likely to benefit from regular endoscopic surveillance. The purpose of surveillance is to detect esophageal adenocarcinoma at an early stage so that cure by surgical resection is likely (20, 21, 23–25, 27). Although the value of endoscopic surveillance programs remains to be proven in large randomized, controlled trials, small observational studies suggest that they result in longer survival after the diagnosis of cancer (20–22). More frequent surveillance is recommended for patients with long-segment Barrett esophagus and dysplasia than for those with metaplasia alone (20, 21, 23, 24, 26, 32). However, the appropriate surveillance interval for patients with short-segment Barrett esophagus, particularly those without dysplasia, remains uncertain (23).

The results of our study indicate that patients with high-grade dysplasia in Barrett esophagus have a greatly increased risk for progression to esophageal adenocarcinoma regardless of segment length. Our data also suggest that the cancer risk among patients with short-segment Barrett esophagus who do not have high-grade dysplasia is not substantially lower than that among patients with long-segment Barrett esophagus who have similar histologic diagnoses. Because these observations are based on

small numbers, firm recommendations on the long-term care of patients with short-segment Barrett esophagus would be premature. Until further data are available, the frequency of endoscopic surveillance should be selected without regard to segment length.

From Fred Hutchinson Cancer Research Center and University of Washington, Seattle, Washington

Acknowledgments: The authors thank Dr. Patricia Blount for her contributions to patient care in the Seattle Barrett's Esophagus Project, Ms. Carissa Sanchez for flow cytometric analyses, Mr. David Cowan and Ms. Janine Kikuchi for database management, Ms. Christine Karlsen and Ms. Sue Irvine for their contributions as patient care coordinators, and Ms. Tricia Christopherson for management of patient interviews.

Grant Support: By National Institutes of Health grants R01 CA61202 and R25 CA57734.

Requests for Single Reprints: Rebecca E. Rudolph, MD, MPH, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, MP-474, Box 19024, Seattle, WA 98109-1024.

Requests To Purchase Bulk Reprints (minimum, 100 copies): Barbara Hudson, Reprints Coordinator; phone, 215-351-2657; e-mail, bhudson@mail.acponline.org.

Current Author Addresses: Drs. Rudolph, Vaughan, Storer, and Reid: Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, MP-474, Box 19024, Seattle, WA 98109-1024. Dr. Haggitt: University of Washington Medical Center, Pathology, BB-210B, Box 356100, Seattle, WA 98195. Dr. Rabinovitch: University of Washington, K-081 Health Sciences Pathology, Box 357470, Seattle, WA 98195. Dr. Levine: AstraZeneca Pharmaceuticals, 725 Chesterbrook Boulevard, E-2C, Wayne, PA 19087-5677.

Author Contributions: Conception and design: R.E. Rudolph, T.L. Vaughan, D.S. Levine, B.J. Reid.

Analysis and interpretation of the data: R.E. Rudolph, T.L. Vaughan, B.E. Storer, R.C. Haggitt, P.S. Rabinovitch, D.S. Levine, B.J. Reid.

Drafting of the article: R.E. Rudolph, T.L. Vaughan.

Critical revision of the article for important intellectual content: R.E. Rudolph, T.L. Vaughan, B.E. Storer, R.C. Haggitt, P.S. Rabinovitch, D.S. Levine, B.J. Reid.

Final approval of the article: R.E. Rudolph, T.L. Vaughan, B.E. Storer, R.C. Haggitt, P.S. Rabinovitch, D.S. Levine, B.J. Reid.

Provision of study materials or patients: T.L. Vaughan, R.C. Haggitt, D.S. Levine, B.J. Reid.

Statistical expertise: R.E. Rudolph, T.L. Vaughan, B.E. Storer. Obtaining of funding: T.L. Vaughan, P.S. Rabinovitch, B.J. Reid. Administrative, technical, or logistic support: T.L. Vaughan, P.S. Rabinovitch, B.J. Reid.

Collection and assembly of data: R.E. Rudolph, T.L. Vaughan, R.C. Haggitt, P.S. Rabinovitch, D.S. Levine, B.J. Reid.

References

1. Fitzgerald RC, Triadafilopoulos G. Recent developments in the molecular characterization of Barrett's esophagus. *Dig Dis*. 1998;16:63-80.
2. Spechler SJ, Zeroogian JM, Antonioli DA, Wang HH, Goyal RK. Prevalence of metaplasia at the gastro-oesophageal junction. *Lancet*. 1994;344:1533-6.
3. Weston AP, Krmpotic P, Makdisi WF, Cherian R, Dixon A, McGregor DH, et al. Short segment Barrett's esophagus: clinical and histological features, associated endoscopic findings, and association with gastric intestinal metaplasia. *Am J Gastroenterol*. 1996;91:981-6.
4. Morales TG, Sampliner RE, Bhattacharyya A. Intestinal metaplasia of the gastric cardia. *Am J Gastroenterol*. 1997;92:414-8.
5. Hirota WK, Loughney TM, Lazas DJ, Maydonovitch CL, Rholl V, Wong RK. Specialized intestinal metaplasia, dysplasia, and cancer of the esophagus and esophagogastric junction: prevalence and clinical data. *Gastroenterology*. 1999;116:277-85.
6. Johnston MH, Hammond AS, Laskin W, Jones DM. The prevalence and clinical characteristics of short segments of specialized intestinal metaplasia in the distal esophagus on routine endoscopy. *Am J Gastroenterol*. 1996;91:1507-11.
7. Chalasani N, Wo JM, Hunter JG, Waring JP. Significance of intestinal metaplasia in different areas of esophagus including esophagogastric junction. *Dig Dis Sci*. 1997;42:603-7.
8. Hameeteman W, Tytgat GN, Houthoff HJ, van den Tweel JG. Barrett's esophagus: development of dysplasia and adenocarcinoma. *Gastroenterology*. 1989;96:1249-56.
9. Miros M, Kerlin P, Walker N. Only patients with dysplasia progress to adenocarcinoma in Barrett's oesophagus. *Gut*. 1991;32:1441-6.
10. Williamson WA, Ellis FH Jr, Gibb SP, Shahian DM, Aretz HT, Heatley GJ, et al. Barrett's esophagus. Prevalence and incidence of adenocarcinoma. *Arch Intern Med*. 1991;151:2212-6.
11. van der Burgh A, Dees J, Hop WC, van Blankenstein M. Oesophageal cancer is an uncommon cause of death in patients with Barrett's oesophagus. *Gut*. 1996;39:5-8.
12. Spechler SJ, Goyal RK. The columnar-lined esophagus, intestinal metaplasia, and Norman Barrett. *Gastroenterology*. 1996;110:614-21.
13. Iftikhar SY, James PD, Steele RJ, Hardcastle JD, Atkinson M. Length of Barrett's oesophagus: an important factor in the development of dysplasia and adenocarcinoma. *Gut*. 1992;33:1155-8.
14. Menke-Pluyers MB, Hop WC, Dees J, van Blankenstein M, Tilanus HW. Risk factors for the development of an adenocarcinoma in columnar-lined (Barrett) esophagus. The Rotterdam Esophageal Tumor Study Group. *Cancer*. 1993;72:1155-8.
15. Hamilton SR, Smith RR, Cameron JL. Prevalence and characteristics of Barrett esophagus in patients with adenocarcinoma of the esophagus or esophagogastric junction. *Hum Pathol*. 1988;19:942-8.
16. Schnell TG, Sontag SJ, Chejfec G. Adenocarcinomas arising in tongues or short segments of Barrett's esophagus. *Dig Dis Sci*. 1992;37:137-43.
17. Cameron AJ, Lomboy CT, Pera M, Carpenter HA. Adenocarcinoma of the esophagogastric junction and Barrett's esophagus. *Gastroenterology*. 1995;109:1541-6.
18. Sharma P, Morales TG, Bhattacharyya A, Garewal HS, Sampliner RE. Dysplasia in short-segment Barrett's esophagus: a prospective 3-year follow-up. *Am J Gastroenterol*. 1997;92:2012-6.
19. Farrow DC, Vaughan TL. Determinants of survival following the diagnosis of esophageal adenocarcinoma (United States). *Cancer Causes Control*. 1996;7:322-7.
20. Streitz JM Jr, Andrews CW Jr, Ellis FH Jr. Endoscopic surveillance of Barrett's esophagus. Does it help? *J Thorac Cardiovasc Surg*. 1993;105:383-7.
21. Lerut T, Coosemans W, Van Raemdonck D, Dillemans B, De Leyn P, Marnette JM, et al. Surgical treatment of Barrett's carcinoma. Correlations between morphologic findings and prognosis. *J Thorac Cardiovasc Surg*. 1994;107:1059-65.
22. Rusch VW, Levine DS, Haggitt R, Reid BJ. The management of high grade dysplasia and early cancer in Barrett's esophagus. A multidisciplinary problem. *Cancer*. 1994;74:1225-9.
23. Sampliner RE. Practice guidelines on the diagnosis, surveillance, and therapy of Barrett's esophagus. The Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol*. 1998;93:1028-32.
24. Cameron AJ. Management of Barrett's esophagus. *Mayo Clin Proc*. 1998;73:457-61.
25. Riddell RH. Early detection of neoplasia of the esophagus and gastroesophageal junction. *Am J Gastroenterol*. 1996;91:853-63.
26. Beck IT, Champion MC, Lemire S, Thomson AB, Anvari M, Armstrong D, et al. The Second Canadian Consensus Conference on the management of patients with gastroesophageal reflux disease. *Can J Gastroenterol*. 1997;11(Suppl B):7B-20B.
27. Reid BJ, Barrett MT, Galipeau PC, Sanchez CA, Neshat K, Cowan DS, et al. Barrett's esophagus: ordering the events that lead to cancer. *Eur J Cancer Prev*. 1996;5(Suppl 2):57-65.
28. Harle IA, Finley RJ, Belsheim M, Bondy DC, Booth M, Lloyd D, et al. Management of adenocarcinoma in a columnar-lined esophagus. *Ann Thorac Surg*. 1985;40:330-6.
29. Streitz JM Jr, Ellis FH Jr, Gibb SP, Balogh K, Watkins E Jr. Adenocarcinoma in Barrett's esophagus. A clinicopathologic study of 65 cases. *Ann Surg*. 1991;213:122-5.
30. Achkar E, Carey W. The cost of surveillance for adenocarcinoma complicating Barrett's esophagus. *Am J Gastroenterol*. 1988;83:291-4.
31. Provenzale D, Kemp JA, Arora S, Wong JB. A guide for surveillance of patients with Barrett's esophagus. *Am J Gastroenterol*. 1994;89:670-80.
32. Reid BJ, Blount PL, Rubin CE, Levine DS, Haggitt RC, Rabinovitch PS. Flow-cytometric and histological progression to malignancy in Barrett's esophagus: prospective endoscopic surveillance of a cohort. *Gastroenterology*. 1992;102:1212-9.
33. Levine DS, Reid BJ. Endoscopic biopsy technique for acquiring larger mucosal samples. *Gastrointest Endosc*. 1991;37:332-7.
34. Reid BJ, Haggitt RC, Rubin CE, Rabinovitch PS. Barrett's esophagus. Correlation between flow cytometry and histology in detection of patients at risk for adenocarcinoma. *Gastroenterology*. 1987;93:1-11.
35. Levine DS, Haggitt RC, Blount PL, Rabinovitch PS, Rusch VW, Reid BJ. An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. *Gastroenterology*. 1993;105:40-50.

36. Reid BJ, Haggitt RC, Rubin CE, Roth G, Surawicz CM, Van Belle G, et al. Observer variation in the diagnosis of dysplasia in Barrett's esophagus. *Hum Pathol.* 1988;19:166-78.
37. Chow WH, Blot WJ, Vaughan TL, Risch HA, Gammon MD, Stanford JL, et al. Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst.* 1998;90:150-5.
38. Stata Statistical Software: Release 5.0. College Station, TX: Stata Corp.; 1997.
39. Weston AP, Krmopotich PT, Cherian R, Dixon A, Topalovski M. Prospective long-term endoscopic and histological follow-up of short segment Barrett's esophagus: comparison with traditional long segment Barrett's esophagus. *Am J Gastroenterol.* 1997;92:407-13.
40. Banerjee B, Salian N, Waits W, Ringold A, Rashid S. Risk factors for developing dysplasia or adenocarcinoma in Barrett's esophagus (BE) with implications for endoscopic surveillance [Abstract]. *Gastroenterology.* 1994;106:A45.
41. Ransom JM, Patel GK, Clift SA, Womble NE, Read RC. Extended and limited types of Barrett's esophagus in the adult. *Ann Thorac Surg.* 1982;33:19-27.
42. Reid BJ, Sanchez CA, Blount PL, Levine DS. Barrett's esophagus: cell cycle abnormalities in advancing stages of neoplastic progression. *Gastroenterology.* 1993;105:119-29.
43. Hong MK, Laskin WB, Herman BE, Johnston MH, Vargo JJ, Steinberg SM, et al. Expansion of the Ki-67 proliferative compartment correlates with degree of dysplasia in Barrett's esophagus. *Cancer.* 1995;75:423-9.
44. Terpstra OT, Dahl EP, Williamson RC, Ross JS, Malt RA. Colostomy closure promotes cell proliferation and dimethylhydrazine-induced carcinogenesis in rat distal colon. *Gastroenterology.* 1981;81:475-80.
45. Kingsnorth AN, King WW, Diekema KA, McCann PP, Ross JS, Malt RA. Inhibition of ornithine decarboxylase with 2-difluoromethylornithine: reduced incidence of dimethylhydrazine-induced colon tumors in mice. *Cancer Res.* 1983;43:2545-9.
46. Ames BN, Gold LS. Too many rodent carcinogens: mitogenesis increases mutagenesis. *Science.* 1990;249:970-1.
47. Menke-Pluymers MB, Mulder AH, Hop WC, van Blankenstein M, Tilanus HW. Dysplasia and aneuploidy as markers of malignant degeneration in Barrett's oesophagus. The Rotterdam Oesophageal Tumour Study Group. *Gut.* 1994;35:1348-51.
48. Kim SL, Waring JP, Spechler SJ, Sampliner RE, Doos WG, Krol WF, et al. Diagnostic inconsistencies in Barrett's esophagus. Department of Veterans Affairs Gastroesophageal Reflux Study Group. *Gastroenterology.* 1994;107:945-9.

Personae

In an effort to bring people to the pages of *Annals*, the editors invite readers to submit photographs of people for publication. We are looking for photographs that catch people in the context of their lives and that capture personality. *Annals* will publish photographs in black and white, and black-and-white submissions are preferred. We will also accept color submissions, but the decision to publish a photograph will be made after the image is converted to black and white. Slides or prints are acceptable. Print sizes should be standard (3" × 5", 4" × 6", 5" × 7", 8" × 10"). Photographers should send two copies of each photograph. We cannot return photographs, regardless of publication. We must receive written permission to publish the photograph from the subject (or subjects) of the photograph or the subject's guardian if he or she is a child. A cover letter assuring no prior publication of the photograph and providing permission from the photographer for *Annals* to publish the image must accompany all submissions. The letter must also contain the photographer's name, academic degrees, institutional affiliation, mailing address, and telephone and fax numbers.

We look forward to receiving your photographs.

Christine Laine, MD, MPH
Deputy Editor