

# Dysplasia and Risk of Further Neoplastic Progression in a Regional Veterans Administration Barrett's Cohort

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- OBJECTIVES:** No published data are available on the risk of further neoplastic progression in Barrett's patients stratified by baseline dysplasia status. Our aims were to estimate and compare the risk of progression to high-grade dysplasia or cancer in groups of Barrett's patients stratified by baseline dysplasia status.
- METHODS:** Consecutive Barrett's cases from 1988–2002 were identified via pathology databases in a regional VA health-care system and medical record data were abstracted. The risk of progression to high-grade dysplasia or cancer was measured and compared in cases with versus without low-grade dysplasia within 1 yr of index endoscopy using survival analysis.
- RESULTS:** A total of 575 Barrett's cases had 2,775 patient-years of follow-up. There were 13 incident cases of high-grade dysplasia and two of cancer. The crude rate of high-grade dysplasia or cancer was 1 of 78 patient-years for those with baseline dysplasia versus 1 of 278 patient-years for those without ( $p = 0.001$ ). One case of high-grade dysplasia in each group underwent successful therapy. One incident cancer case underwent successful resection and the other was unresectable. Two cases with high-grade dysplasia later developed cancer, one died postoperatively, the other was unresectable. When these two cases were included (total of four cancers), the crude rate of cancer was 1 of 274 patient-years for those with baseline dysplasia versus 1 of 1,114 patient-years for those without.
- CONCLUSIONS:** In a large cohort study of Barrett's, incident malignancy was uncommon. The rate of progression to high-grade dysplasia or cancer was significantly higher in those with baseline low-grade dysplasia. These data may warrant reevaluation of current Barrett's surveillance strategies.

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## INTRODUCTION

Barrett's esophagus is an acquired condition characterized by specialized intestinal metaplasia of the esophagus (1, 2). Patients with Barrett's esophagus are at increased risk of developing esophageal adenocarcinoma, and periodic endoscopic surveillance with random esophageal biopsies to detect high-grade dysplasia or early cancer is the standard of care (3). The cost-effectiveness of surveillance is critically dependent on the estimated magnitude of risk for further neoplastic progression, yet this risk remains uncertain (4, 5). Risk estimates from previously published observational studies are difficult to interpret for a number of reasons, including varying definitions of Barrett's esophagus (*e.g.*, histologic type, length of segment), varying definitions of cancer (*e.g.*, esophageal, cardia), selection bias, publication bias, and lack of distinction between incident and prevalent cases

of high-grade dysplasia or cancer (6). Most observational study cohorts are small, selected groups from Barrett's referral centers. Perhaps the greatest limitation of these studies is their failure to report and compare incidence rates for further neoplastic progression using patient strata defined by putative risk factors such as the presence of low-grade dysplasia at baseline (7–20).

Barrett's esophagus is thought to sequentially progress from metaplasia without dysplasia, to low-grade dysplasia, to high-grade dysplasia, and then to adenocarcinoma. The time sequence of this progression and the factors involved in initiation/promotion remain unknown. The molecular correlates of this progression are poorly characterized and biomarkers (*e.g.*, aneuploidy, oncogenes, tumor-suppressor genes, or markers of proliferation) are not yet reliable enough to be clinically useful or demonstrably better than histology in assessing risk of progression (17, 21–31). The presence and

grade of histologic dysplasia in random esophageal biopsies obtained from periodic endoscopic surveillance exams remains the most widely used marker of a further increase in malignant risk among those with Barrett's esophagus, but the level of increased risk is difficult to quantify based on published data (32–34). It has been suggested that patients without dysplasia at baseline may not warrant surveillance, since cases only rarely progress to high-grade dysplasia or cancer during follow-up (5). However, no prior study has compared incidence rates in Barrett's cases stratified by baseline dysplasia status. We, therefore, compared incidence rates for the development of high-grade dysplasia or cancer in a well-defined Veterans Administration (VA) Barrett's cohort stratified by baseline low-grade dysplasia status.

## METHODS

### Setting

The Southern California Regional VA Healthcare System (VA Integrated Service Network 22, or VISN 22) is comprised of four major medical centers (Greater Los Angeles, Loma Linda, Long Beach, San Diego) and multiple satellite clinics throughout southern California and Nevada. All four major medical centers have accredited postgraduate training programs in surgery, pathology, and gastroenterology. The medical record system, while not directly linked at the time of this study, is nearly identical across centers. The patient population consists predominantly of older White men, although there is some variation across centers.

During the study time frame there were no regional or center-specific guidelines for the management of patients with Barrett's esophagus. Endoscopic surveillance of patients with Barrett's esophagus in VISN 22 is predominantly performed by gastroenterologists and surgeons at the major medical centers, although some procedures are performed at satellite facilities. Gastroenterologic pathology specimens from all sites are submitted to pathology laboratories at the major medical centers for processing, interpretation, and inclusion in electronic databases using standardized topographic and histologic codes from the Systematized Nomenclature of Human and Veterinary Medicine (SNOMED) classification system (35).

### Study Design

This is a historical cohort study using existing medical record data to examine rates of incident cancer or high-grade dysplasia for patients with known Barrett's esophagus when stratified by baseline dysplasia status. This study was approved by the Office for the Protection of Research Subjects at each of the participating centers.

### Case Identification

Potential cases were identified via an electronic search of pathology databases at each of the four major VISN 22 medical centers from January 1988 to May 2002 using standardized (SNOMED) morphology codes for gas-

tric metaplasia (73330), and topography codes for esophagus/gastroesophageal junction (62XXX). Medical records of all potential cases were then reviewed to identify those with pathology reports specifying the presence of specialized intestinal metaplasia (*e.g.*, goblet cells, specialized epithelium) in esophageal biopsy specimens.

### Data Collection

Medical record data for all potential cases were abstracted by three investigators (GD, JC, DO) using a standardized data collection form. The date of transition from paper to electronic medical record data collection system varied from center to center, as did the integration of electronic endoscopic databases into the main system. Thus, sources of local medical record data included the paper chart, the electronic chart, electronic endoscopic databases, paper pathologic records, and paper research charts when available. Medical record data were reviewed to identify the first endoscopic biopsy indicative of Barrett's esophagus, subsequently referred to as the index exam, and all subsequent exams. A test set of 10 randomly selected potential cases was reviewed by all abstractors in a blinded fashion to test interrater reliability for presence/absence of Barrett's, baseline dysplasia, and/or high-grade dysplasia/cancer. There was a 100% concordance between investigators with regard to the three variables of primary interest in the test set. The majority (52%) of all 844 potential cases identified were reviewed by one investigator (GD), 27% by another (JC), and 21% by the third (DO).

A form was completed for each case using pathology reports for histologic data (*e.g.*, epithelial types present, presence/absence and grade of dysplasia), endoscopic reports for endoscopic data (*e.g.*, indication for endoscopy, length of Barrett's esophagus segment, presence of hiatal hernia), and physician or nursing notes for age, ethnicity, gastroesophageal reflux disease symptoms (*e.g.*, heartburn, regurgitation), smoking history, alcohol history, weight, height, and family history of gastrointestinal cancer. The endoscopic length of the Barrett's segment was determined by subtracting the level of the gastroesophageal junction from the uppermost level of the squamo-columnar junction (Z-line) when recorded, or the length of the segment as reported by the endoscopist in the medical record. Data on the use of selected medications (*e.g.*, proton pump inhibitors, histamine-type 2 receptor antagonists) at the time of diagnosis were obtained from the physician/nurse notes or pharmacy records. When data were discrepant, preference was given to the findings recorded closest to the date of the index exam.

The date and cause of death, or the date of last recorded clinical follow-up in VISN 22 was initially determined by review of local medical record data. These data were then linked to the national VA BIRLS (Beneficiary Identification and Records Locator System) file. The BIRLS file is a reliable and valid indicator of mortality among veterans (36). Data were also linked to California's Confidential Vital Statistics Death File. Local medical record data were linked to BIRLS and California's Death Files in order to validate vital status information and extend case mortality findings.

### ***Inclusion and Exclusion Criteria***

To be included in the study, cases had to have medical records specifying the presence of specialized intestinal metaplasia (e.g., goblet cells, specialized epithelium) in esophageal biopsy specimens. Cases whose medical records indicated the presence of high-grade dysplasia or cancer in esophageal biopsy specimens taken within 1 yr of the index exam were classified as prevalent high-grade dysplasia/cancer cases and excluded.

### ***Measures of Risk for Malignant Progression***

Included cases were stratified according to their baseline dysplasia status. Cases with medical record data indicating any grade of dysplasia other than high (e.g., indefinite, low, or moderate, all of which may be consistent with modern definitions of low-grade dysplasia) on any esophageal biopsy taken within 1 yr of the index exam were classified as having low-grade dysplasia at baseline, according to current terminology (37).

### ***Measures of Outcome***

Cases of high-grade dysplasia or cancer detected greater than 1 yr after the index VA exam were classified as incident cases to avoid misclassification of prevalent cases. The duration of follow-up was equal to the time from the index exam to the date of high-grade dysplasia/cancer diagnosis, death, or last known VA clinical follow-up. Death was attributed to esophageal cancer if this disease was listed as a proximate cause in the medical record (e.g., death certificate).

### ***Data Analysis***

All data from the study forms were entered into a computer file. SAS (Version 8.0, SAS Institute, Carey, NC) was used for data management and analysis. Missing or inconsistent data were addressed by a standardized series of checks and corrections.

The primary outcome measure was the risk of developing esophageal adenocarcinoma or high-grade dysplasia, estimated using the product-limit (Kaplan-Meier) method. Survival (time to event) curves for the group with baseline low-grade dysplasia were compared to the group without baseline dysplasia using corresponding log rank tests at the  $p < 0.05$  level of significance.

Included cases with low-grade dysplasia at baseline were compared to those without baseline dysplasia with regard to baseline characteristics. Crude high-grade dysplasia/cancer rates are presented as cases per patient-years of follow-up. The density method was also used to estimate cumulative disease risk over time. This method assumes that the time to event has an exponential distribution, which is equivalent to assuming that the disease rate (hazard) is constant over time. Means were compared using Student's *t*-test, proportions were compared using  $\chi^2$  methods, and the Wilcoxon rank sum test was used to compare medians. A two-sided *p*-value less than 0.05 was considered statistically significant.

### ***Role of the Funding Source***

The funding source had no direct role in the design, data collection, analysis, or decision to submit the paper for publication.

## **RESULTS**

### ***Study Population***

Eight-hundred and forty-four potential cases of Barrett's esophagus were identified via electronic searches of pathology databases in the Southern California Regional Veterans Administration Healthcare System (VISN 22) from 1988–2002 (Fig. 1). After excluding those with baseline high-grade dysplasia or cancer, 575 cases of Barrett's esophagus were available for analysis in this study. These cases underwent 1,954 upper endoscopies with 10,136 esophageal biopsies over 2,775 patient-years of follow-up.

### ***Patient Demographics***

The majority of included cases were older White men who drank alcohol and smoked (Table 1). The majority also had a recorded history of heartburn or dysphagia, and had received a prescription for a proton pump inhibitor (23%) or histamine type 2 receptor antagonist (28%) prior to the index exam. A finding of esophagitis was reported in 29% of initial endoscopies. Two-thirds (66.7%) of all included cases were noted to have a hiatal hernia. Cases underwent a mean of 1.4 endoscopic examinations within the first year after diagnosis of Barrett's esophagus.

Nearly one-quarter (23%) of all included cases had low-grade dysplasia at baseline. The proportion of all included patients with baseline dysplasia did not vary substantially across centers (data not shown). Cases with baseline low-grade dysplasia were more likely to be White than those without baseline dysplasia ( $p = 0.03$ ). Cases with baseline dysplasia were less likely ( $p = 0.031$ ) to present with dysphagia than those without baseline dysplasia, and had a lower mean number of endoscopic exams (1.4 vs 1.7) performed within 1 yr of the index exam ( $p < 0.001$ ). There were no other statistically significant differences between groups in any other measured baseline variables. The percentage with a prescription for a proton pump inhibitor prior to diagnosis was 27% in those with baseline low-grade dysplasia versus 22% in those without baseline dysplasia ( $p = 0.242$ ). The percentage with esophagitis noted on initial endoscopy did not differ significantly ( $p = 0.494$ ) between those with baseline dysplasia (27%) and those without (30%). The mean length of the Barrett's segment did not vary between those with (7.4 cm) versus those without (6.5 cm) baseline low-grade dysplasia ( $p = 0.164$ ). The presence of a hiatal hernia was noted in 69% of those with baseline dysplasia versus 66% of those without baseline dysplasia ( $p = 0.526$ ). The mean number of esophageal biopsies taken per initial endoscopy in those who were found to have baseline dysplasia (mean = 4.6 biopsies) was similar ( $p = 0.10$ ) to the number taken in those were found not to have baseline dysplasia (mean = 4.0).

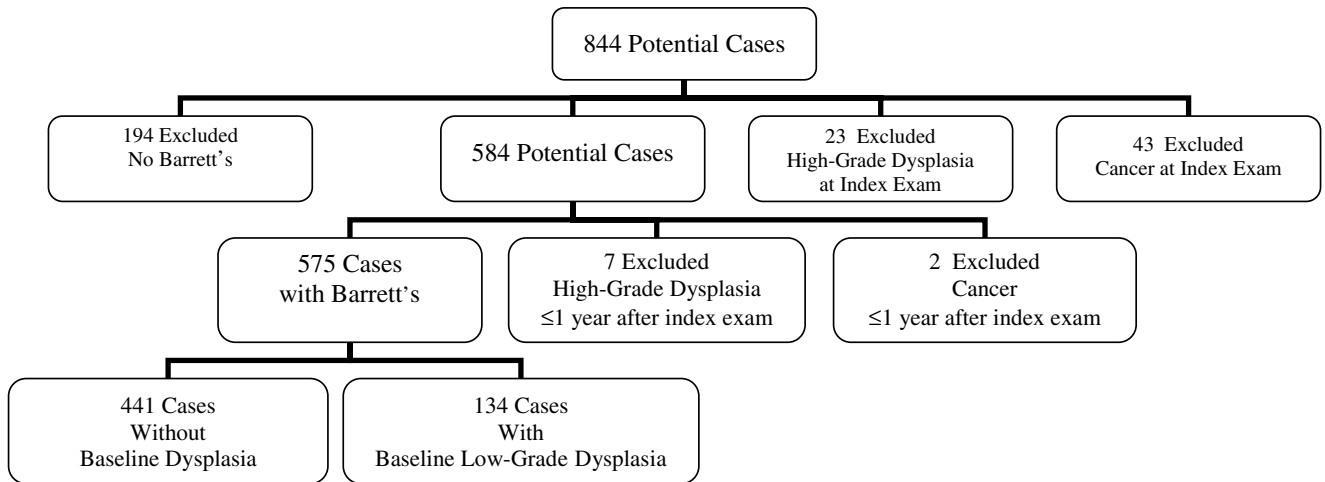


Figure 1. Flow diagram.

The median number of patient-years of follow-up were similar ( $p = 0.247$ ) in those with baseline low-grade dysplasia (3.21 yr) and those without baseline dysplasia (3.67 yr). The median number of endoscopic exams performed during follow-up were also similar ( $p = 0.201$ ) in those with baseline dysplasia (three exams) and those without baseline dysplasia (two exams). The mean number of esophageal biopsies taken per endoscopy per person during follow-up was greater ( $p < 0.001$ ) in those with (mean = 5.8) compared to those without (mean = 3.6) baseline dysplasia. However, the proportion of exams in which random four-quadrant biopsies were reported to have been taken from at least every 2 cm of the Barrett's segment were similar ( $p = 0.55$ ) for those with (30%) and those without (31%) baseline dysplasia.

**Incidence of High-Grade Dysplasia and Cancer**

There were 13 incident cases of high-grade dysplasia and 2 incident cases of cancer among the 575 study cases in 2,775 patient-years of follow-up. All cases occurred in White men with a mean age of 62 yr at the time of Barrett's esophagus diagnosis, and a mean age of 70 yr at the time of high-grade dysplasia/cancer diagnosis. The time course from diagnosis of Barrett's esophagus to diagnosis of high-grade dys-

plasia/cancer for all 15 incident cases is shown in Figure 2. The median (interquartile range = IQR) latent period for progression from Barrett's esophagus to high-grade dysplasia or cancer was 2.75 (2.50–11.51) yr for those with baseline low-grade dysplasia, which was significantly shorter ( $p = 0.037$ ) than the 9.88 (5.84–14.22) yr for those without baseline dysplasia.

Crude high-grade dysplasia/cancer incidence rates by baseline low-grade dysplasia status are shown in Table 2. The crude rate of high-grade dysplasia/cancer for those with baseline low-grade dysplasia was 1 of 78 patient-years of follow-up versus 1 of 278 patient-years of follow-up for those without baseline dysplasia ( $p = 0.0011$ ). Survival (or time to development of high-grade dysplasia/cancer) curves for groups of cases with versus without baseline dysplasia are shown in Figure 3. We cannot definitively address statistical differences in crude incidence rates across VA centers since this study was not powered to detect such differences. However, we did not find any substantial descriptive differences across the four centers studied (data not shown). Among those with baseline dysplasia, there was no difference in the crude rate of high-grade dysplasia/cancer for those

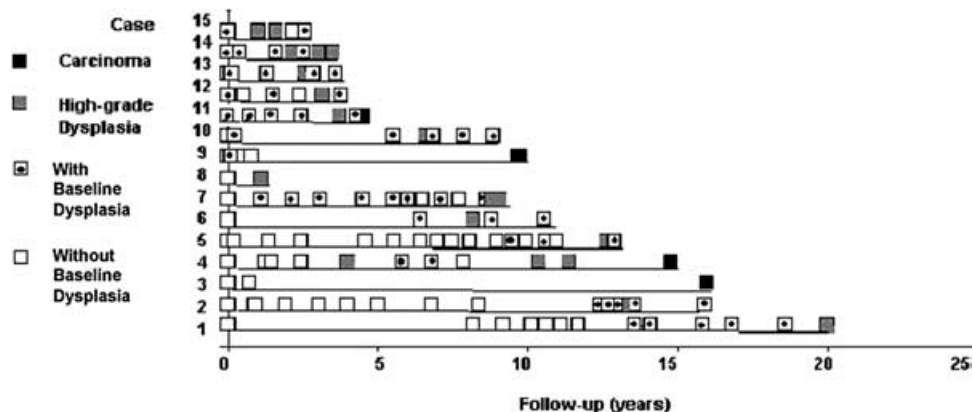
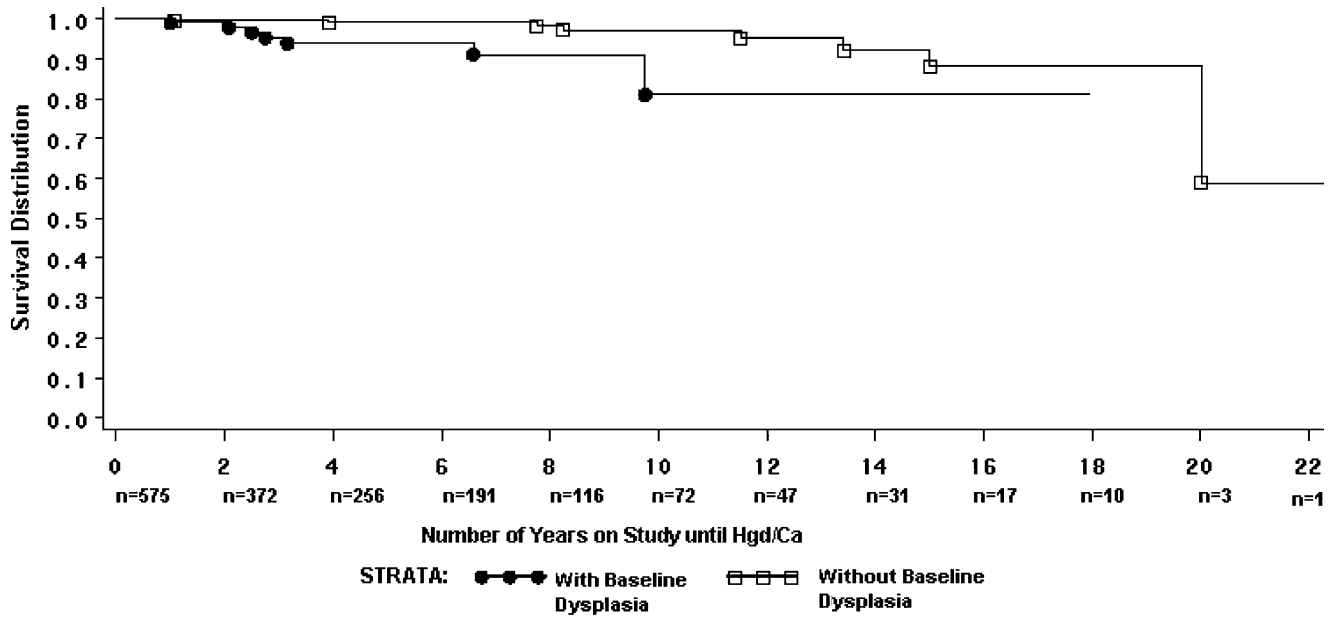


Figure 2. Course of surveillance for 15 incident cases of high-grade dysplasia or cancer. Case 5 underwent endoscopic mucosal resection, while case 15 underwent endoscopic ablation therapy.



**Figure 3.** Time to development of high-grade dysplasia or cancer (survival curves) for cases with baseline low-grade dysplasia *versus* those without baseline dysplasia. The crude incidence rate of high-grade dysplasia or cancer for those with baseline dysplasia was 1 of 78 patient-years of follow-up *versus* 1/278 patient-years of follow-up for those without baseline dysplasia ( $p = 0.0011$  for log-rank test).

with *versus* without esophagitis noted on initial endoscopy (data not shown).

Over a median (IQR) of 3.9 (2.5–8.3) patient-years of follow-up 2 of 13 (15.4%) cases with incident high-grade dysplasia subsequently progressed to cancer. When these two cases were included (for an overall total of four cancers), the overall crude rate of cancer was 1 of 694 patient-years of follow-up, or 1 of 274 patient-years of follow-up for those with baseline low-grade dysplasia *versus* 1 of 1,114 patient-years of follow-up for those without baseline dysplasia ( $p = 0.1791$ ). The natural history of two additional cases of incident high-grade dysplasia is unknown due to therapeutic intervention: one case with dysplasia at baseline entered a trial of ablation therapy with multipolar electrocoagulation, and one case without dysplasia at baseline underwent endoscopic mucosal resection. If it is assumed that these cases would have progressed to cancer within the study time frame, then the adjusted crude rate of cancer would have been 1 of 184 patient-years for those with baseline low-grade dysplasia *versus* 1 of 742 patient-years for those without baseline dysplasia ( $p = 0.0976$ ).

**Outcomes**

Of the two cases with incident cancer, one case (with baseline low-grade dysplasia) underwent successful resection with surgical pathology revealing carcinoma *in situ* and was alive with no evidence of disease 3 yr later, the other (without baseline dysplasia) was given a clinical stage of T3N1, refused treatment, and was lost to medical record follow-up. Of the two cases with incident high-grade dysplasia who later developed cancer, one (with baseline dysplasia) died due to postoperative complications 8 months after resection with surgical pathology revealing a T2N0 lesion, the other (without baseline dysplasia) had a clinical stage T4N1 and died of disease in 11 months.

One-quarter (146/575) of included cases died during follow-up. The proportion of subjects dying was similar in the group with baseline dysplasia (31/134 = 23%) and that without baseline dysplasia (115/442 = 26%). The mean age at death was 70 yr. Based-on the medical record data we collected, two deaths were attributable to esophageal adenocarcinoma. Comparison of the electronic BIRLS database to study data obtained from the local medical record review revealed

**Table 1.** Baseline Demographic Data for Study Cohort by Risk Group

Baseline Dysplasia Status	N*	Male (%)	White <sup>†</sup> (%)	Age (Years) <sup>‡</sup>	BMI (Kg/M2) <sup>‡</sup>	Alcohol Use (%)	Tobacco Use (%)	Heartburn (%)	Dysphagia <sup>†</sup> (%)
Negative	441	99	83	59 ± 12	27 ± 5	70	71	43	27
Positive	134	98	91	61 ± 12	28 ± 6	67	68	43	18
TOTAL	575	99	85	60 ± 12	28 ± 5	69	71	43	25

Cases positive for baseline low-grade dysplasia were defined by pathology reports indicating esophageal biopsies having any grade of dysplasia other than high-grade (*i.e.*, indefinite, low, moderate) within 1 yr of the diagnosis of Barrett's esophagus.

\*N varies slightly by item due to missing values.

<sup>†</sup> $p < 0.05$  for between group comparison.

<sup>‡</sup>Mean ± SD value.

BMI = body mass index.

**Table 2.** Crude High-grade Dysplasia/Cancer Incidence Rates in Barrett's Esophagus Cases Undergoing Surveillance by Baseline Low-grade Dysplasia Status

Baseline Dysplasia Status	N	Patient-Years Follow-Up	Incident Cases High-Grade Dysplasia or Cancer	High-Grade Dysplasia or Cancer Patient-Years of Follow-Up	Incident Cases Cancer*	Cancer/Patient-Years of Follow-Up
Negative	441	2,227	8	1/278	2	1/1,114
Positive	134	548	7	1/78	2	1/274
Total	575	2,775	15	1/185	4	1/694

\*Includes two cases with incident high-grade dysplasia who later progressed to cancer. Excludes two cases with high-grade dysplasia in whom the natural history of disease was interrupted by therapeutic interventions. See text for details.

no additional cases of mortality during the study timeframe. Comparison of California's Vital Statistics Death Files to our study data revealed 18 additional cases of mortality—5 with baseline low-grade dysplasia and 13 without baseline dysplasia. In all 18 cases, the date of last VA follow-up preceded the date of death as recorded in the California Vital Statistics Death File. One case with baseline low-grade dysplasia was lost to VA medical record follow-up after the diagnosis of advanced (T3N1) esophageal adenocarcinoma, but listed as dead of disease 10 days later in the California Vital Statistics Death File. Considering all available sources of mortality data, 164 of 575 (29%) of all included cases died during extended follow-up, with 3 of 164 (2%) of all deaths attributable to esophageal adenocarcinoma.

## DISCUSSION

The findings of this large cohort study of patients with Barrett's esophagus suggest that low-grade dysplasia in an esophageal biopsy taken within 1 yr of the diagnosis of Barrett's esophagus is associated with a significantly increased risk of further neoplastic progression to high-grade dysplasia or cancer. These data may be particularly relevant to community practice, as opposed to referral centers of excellence, since this cohort represents the experience of unselected patients seen by practicing endoscopists and pathologists. Given the crude incidence rates for development of cancer in this study, a 60-yr-old male veteran with Barrett's epithelium would have a 3.5% chance of developing esophageal adenocarcinoma within 10 yr if he had low-grade dysplasia at baseline *versus* a 0.9% risk of cancer in the absence of baseline dysplasia. Nearly 30% of the study cohort died, on average within 10 yr of Barrett's diagnosis, but only 2% of these deaths were attributable to esophageal adenocarcinoma. There was little evidence to suggest that many of the 575 patients in this cohort benefited from endoscopic surveillance as practiced in this setting, with only one of four incident cancer cases receiving curative therapy. These data may warrant reevaluation of current Barrett's surveillance strategies in which patients without dysplasia undergo endoscopy with biopsies every 2–3 yr.

There are no previously published estimates of malignant risk in Barrett's cohorts stratified by baseline dysplasia status. A recently published decision analysis model used a crude cancer incidence rate of 1 of 200 patient-years for cases

without dysplasia *versus* an unpublished estimate of 1 of 40 patient-years for cases with low-grade dysplasia (5). They concluded that screening 50-yr-old White men with symptoms of heartburn for esophageal adenocarcinoma might be cost-effective if subsequent surveillance were limited to cases with low-grade dysplasia in a segment of Barrett's esophagus detected on the screening exam. The corresponding cancer incidence rates of 1 of 1,114 patient-years *versus* 1 of 274 patient-years in the present study may provide further support for prevention strategies that limit surveillance to cases with low-grade dysplasia.

At first glance, the crude incidence rate of high-grade dysplasia or cancer of 1 of 185 patient-years of follow-up reported in this study is similar to the estimated crude incidence rate of 1 of 200 patient-years of follow-up for cancer alone given in a recent systematic review (6). However, the overall crude incidence rate of 1 of 694 patient-years of follow-up for cancer alone reported in the present study is much lower than previous estimates. This may in part be accounted for by rigid exclusion of prevalent high-grade dysplasia or cancer, and the nature of this unselected, nonreferral-based cohort. The results of this surveillance study, based on the work of practicing VA endoscopists and pathologists, may more closely reflect community cohorts than previously published studies from referral centers of excellence.

Surveillance of Barrett's esophagus is resource intensive, while the direct evidence of benefit to patients is limited (38). As in the present study, most Barrett's-associated cancers are prevalent cases detected outside of surveillance (39). Cancer prevention/detection strategies that incorporate screening may be a cost-effective alternative to surveillance of sporadically detected cases alone, but only if surveillance is limited to high-risk groups, especially in light of recent studies suggesting an unexpectedly high prevalence of Barrett's esophagus in patients undergoing colorectal cancer screening (40, 41). The development of rational, cost-effective strategies for screening and surveillance of Barrett's esophagus requires more accurate estimates of cancer risk overall as well as in strata defined by available clinical markers. Since the majority of Barrett's esophagus patients do not have dysplasia at baseline, confirmation of a low-risk for neoplastic progression in this group would have important implications for esophageal cancer screening and surveillance programs.

This study has some limitations. First, the VA population is demographically skewed and dynamic with many patients seeking care at multiple sites within and outside the system. Loss to follow-up within the system may reduce the sample size (increased random error) and lead to bias (systematic error) in estimating the effect of dysplasia on cancer incidence. Second, the incidence of cancer was too low to allow analytic adjustment for potential confounders such as age, length of Barrett's segment, presence of hiatal hernia, presence of esophagitis at index exam, gender, ethnicity, body mass index, use of selected medications, or duration and severity of gastroesophageal reflux disease symptoms. Third, misclassification of exposure status (*i.e.*, the presence and grade of dysplasia at baseline) or the outcome (*i.e.*, presence of high-grade dysplasia or cancer) may occur because of sampling error inherent in endoscopic surveillance, interobserver variation in interpretation of the histology specimens obtained, or even reactive changes in the setting of active esophagitis (42–47). Intensive surveillance protocols that limit sampling error, though now widely accepted as the standard of care, do not appear to have been followed in most cases over the time period studied (48, 49). Nor was the diagnosis of dysplasia in the present study explicitly validated by subjecting pathology specimens to blinded review by an independent expert. Furthermore, other studies have demonstrated that a finding of dysplasia is transient in many cases (50).

The effects of these limitations on the study results merits further consideration. First, the VA does serve a skewed demographic—primarily older White males—but this may be an advantage because this is the population at greatest risk for Barrett's-associated adenocarcinoma. If anything, results from this population may tend to overestimate the cancer risk in the general population of patients with Barrett's esophagus. The VA population is dynamic, but probably not more so than other populations in southern California. Still, loss to follow-up within the regional VA system could lead to bias in estimating the effect of dysplasia on progression to cancer. Since esophageal adenocarcinoma has a high mortality rate, vital status information obtained by review of local medical records was validated by comparison to the national VA Beneficiary Identification and Records Locator System File as well as California's Vital Statistics Death File. This tends to minimize, but not eliminate, the possibility of missed cancer cases. Although one could postulate that loss to follow-up would be differentially distributed according to baseline dysplasia status and cancer incidence, with those positive for dysplasia being more likely to follow-up, the number of exams and patient-years of follow-up were similar between study groups. Unlike studies from referral centers with an interest in Barrett's, this VA population is unlikely to be enriched with unusual or high-risk cases. The screening and surveillance practices in the VA system may more closely resemble community-based care than referral center care. With over 10,000 esophageal biopsies from nearly 2,000 upper endoscopies in nearly 3,000 patient-years of follow-up,

the surveillance workload was heavy even if not as intensive as some experts recommend. Second, although the sample size did not allow for multivariate analysis, this is still the largest cohort study yet reported. Moreover, univariate analysis did not reveal any striking differences between groups with *versus* without dysplasia at baseline in regard to putative risk factors for baseline dysplasia such as esophagitis, or progression such as age or length of Barrett's segment. Third, many of the factors (*e.g.*, sampling error, interobserver variability) potentially affecting exposure status could have resulted in differential misclassification to absence of baseline dysplasia. However, this would bias the difference in risk between dysplastic and nondysplastic groups towards the null, strengthening the nature of our results. On the other hand, differential misclassification to incident high-grade dysplasia or cancer could bias results away from the null. The nature of our study design does not allow us to definitively exclude the possibility of bias in either direction.

Future studies from other unselected populations should be performed to confirm or refute these results. Ideally, data would come from a prospective, multicenter effectiveness trial with randomization of patients to varying surveillance intervals based on the presence and grade of dysplasia. For the time being, careful initial endoscopy with multiple biopsies should guide management. Health-care systems, like the VA, and the populations they serve may incorporate data from this study in conjunction with data from other populations into medical decision making about the appropriate and necessary use of health-care resources. Given finite health-care resources, these findings suggest that endoscopic surveillance might best be focused on patients with dysplasia detected at or near the time of Barrett's diagnosis who are willing and able to undergo treatment for incident cancer.

## WHAT IS KNOWN AND WHAT THIS STUDY ADDS

1. Patients with Barrett's esophagus are at increased risk of developing esophageal adenocarcinoma, and periodic endoscopic surveillance to detect high-grade dysplasia or early cancer is the standard of care.
2. Endoscopic screening to detect Barrett's, high-grade dysplasia, or early cancer is not as widely practiced as surveillance, and may not be economically feasible without means of stratifying Barrett's cases into low- and high-risk groups at baseline.
3. Most cases of Barrett's associated esophageal adenocarcinoma are not detected through screening/surveillance programs, and most are diagnosed at a late stage with poor prognosis.
4. The finding of low-grade dysplasia in Barrett's is thought to be a marker of increased risk for further neoplastic progression that requires intensive surveillance, yet no large studies have compared the magnitude of risk in groups of Barrett's patients with *versus* without low-grade dysplasia at baseline.

5. In this large cohort of Veterans with Barrett's esophagus, 84% (76/91) of all cases with high-grade dysplasia or cancer were prevalent.
6. The annualized risk of incident high-grade dysplasia or cancer was significantly ( $p = 0.001$ ) higher for those with baseline dysplasia (1.28% per year) than for those without baseline dysplasia (0.36% per year).
7. Given finite health-care resources, these findings suggest that endoscopic surveillance might best be focused on patients with dysplasia detected at or near the time of Barrett's diagnosis who are willing and able to undergo treatment for incident cancer.

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