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Incidence of Adenocarcinoma among Patients with Barrett's Esophagus

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ABSTRACT

BACKGROUND

Accurate population-based data are needed on the incidence of esophageal adenocarcinoma and high-grade dysplasia among patients with Barrett's esophagus.

METHODS

We conducted a nationwide, population-based, cohort study involving all patients with Barrett's esophagus in Denmark during the period from 1992 through 2009, using data from the Danish Pathology Registry and the Danish Cancer Registry. We determined the incidence rates (numbers of cases per 1000 person-years) of adenocarcinoma and high-grade dysplasia. As a measure of relative risk, standardized incidence ratios were calculated with the use of national cancer rates in Denmark during the study period.

RESULTS

We identified 11,028 patients with Barrett's esophagus and analyzed their data for a median of 5.2 years. Within the first year after the index endoscopy, 131 new cases of adenocarcinoma were diagnosed. During subsequent years, 66 new adenocarcinomas were detected, yielding an incidence rate for adenocarcinoma of 1.2 cases per 1000 person-years (95% confidence interval [CI], 0.9 to 1.5). As compared with the risk in the general population, the relative risk of adenocarcinoma among patients with Barrett's esophagus was 11.3 (95% CI, 8.8 to 14.4). The annual risk of esophageal adenocarcinoma was 0.12% (95% CI, 0.09 to 0.15). Detection of low-grade dysplasia on the index endoscopy was associated with an incidence rate for adenocarcinoma of 5.1 cases per 1000 person-years. In contrast, the incidence rate among patients without dysplasia was 1.0 case per 1000 person-years. Risk estimates for patients with high-grade dysplasia were slightly higher.

CONCLUSIONS

Barrett's esophagus is a strong risk factor for esophageal adenocarcinoma, but the absolute annual risk, 0.12%, is much lower than the assumed risk of 0.5%, which is the basis for current surveillance guidelines. Data from the current study call into question the rationale for ongoing surveillance in patients who have Barrett's esophagus without dysplasia. (Funded by the Clinical Institute, University of Aarhus, Aarhus, Denmark.)

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Barrett's esophagus, defined as intestinal metaplasia in the distal esophagus, is considered to be a complication of gastroesophageal reflux disease and a precursor lesion in most cases of esophageal adenocarcinoma.[1] The transition from Barrett's esophagus to adenocarcinoma is believed to progress through low-grade and high-grade dysplasia, thus justifying endoscopic surveillance for these premalignant stages.[2-4] However, an estimated 95% of patients with a new diagnosis of adenocarcinoma do not have a previous diagnosis of Barrett's esophagus.[5-10] Since surveillance programs have never been shown to have any effect on survival, their relevance has been questioned.[7-9,11-16]

Accurate estimates of the annual incidence of adenocarcinoma and high-grade dysplasia among patients with Barrett's esophagus have been difficult to obtain, since studies have shown considerable variation in incidence rates. In two recent reviews, the pooled incidences of adenocarcinoma were estimated to be 5.3 and 6.5 cases per 1000 person-years, whereas the incidence estimates for the combined end point of high-grade dysplasia or adenocarcinoma were 9.1 and 10.2 cases per 1000 person-years.[9,17]

The risk of adenocarcinoma also seems to be associated with increasing age and with male sex.[7,18] However, the majority of studies evaluating these factors have had small samples of selected patients and short follow-up periods. Publication bias may also have occurred.[6,19]

To examine these issues, we conducted a cohort study using population-based data from the Danish Pathology Registry and the Danish Cancer Registry. Specifically, we aimed to calculate the incidence of adenocarcinoma or high-grade dysplasia among patients with Barrett's esophagus, compare this incidence with that expected in the general population, and determine whether low-grade dysplasia detected at the time of a diagnosis of Barrett's esophagus is a risk factor for adenocarcinoma or high-grade dysplasia.

METHODS

PATIENTS AND FOLLOW-UP

We conducted this cohort study within the entire Danish population of 5.4 million persons. Denmark has free, tax-supported health care; therefore, data on hospital services are essentially population-based.

In all Danish medical registries, patients are identified by means of a civil registration number. This number is a unique identifier that is assigned at birth and stored in the Civil Registration System along with date of birth and residency status, as well as dates of immigration or emigration and death.[20] The civil registration number allows unambiguous linkage of individual-level data among registries.

The Danish Pathology Registry contains pathology reports and other information regarding all biopsy specimens examined at all hospitals and by all private practitioners in Denmark.[21] Specimens are categorized according to the Systematized Nomenclature of Medicine (SNOMED) classification. The diagnoses in the registries are made on the basis of histologic specimens, with the sites identified by accompanying text from the clinician and evaluated by specialized pathologists.

We used the Pathology Registry to identify all 11,028 patients in Denmark who underwent endoscopic biopsy and received a diagnosis of Barrett's esophagus, according to SNOMED criteria (SNOMED code T62 in combination with M73320 or M73330). Barrett's esophagus was diagnosed by the presence of specialized intestinal metaplasia in esophageal-biopsy specimens. Patients received free care according to prevailing guidelines at the community-based clinic where they received their usual care.[22,23]

Within this cohort, we also searched the Pathology Registry for cases of low-grade dysplasia (T62 in combination with M74009 or M74A09) and distinguished between cases that were present at the time of the diagnosis of Barrett's esophagus and cases that were diagnosed during the follow-up period. In addition, we identified patients with high-grade dysplasia (T62 in combination with M74B09 or M74C09) and excluded patients with a previous or concurrent diagnosis of high-grade dysplasia at the time they received the diagnosis of Barrett's esophagus.

Using the civil registration numbers, we linked the cohort patients to the Danish Cancer Registry to identify those who, before December 31, 2009, received a diagnosis of esophageal adenocarcinoma (*International Classification of Diseases, 10th Revision* [ICD-10] code C15 in combination with 74C09, 82603, 84803, 84903, 82113, 81433, 73320, 81403, 80702, or 80703). Patients with a previous or concurrent diagnosis of adenocarcinoma were excluded from the cohort. Since 1943, the Danish

Cancer Registry has kept records of all patients in Denmark with malignant neoplasms. Several studies have documented the very high validity and completeness (greater than 98%) of the registry data.[21]

The study was approved by the Danish Data Protection Agency. In accordance with Danish law, approval from an ethics committee and informed consent from the patients were not required for this registry study.

STATISTICAL ANALYSIS

Descriptive data are presented as median values and interquartile ranges. We calculated incidence rates (cases per 1000 person-years) for the three end points — high-grade dysplasia, esophageal adenocarcinoma, and the combined end point of adenocarcinoma or high-grade dysplasia — among patients who had received a diagnosis of Barrett's esophagus and in the general population. The patients were stratified according to the presence or absence of low-grade dysplasia on the index endoscopy and according to status with respect to the development of low-grade dysplasia during follow-up.

Each patient was followed from the date of the diagnosis of Barrett's esophagus until the occurrence of one of the end points or until emigration, death, or the end of December 2009, whichever came first. Incidence rates with 95% confidence intervals were calculated for all end points.

Standardized incidence ratios and 95% confidence intervals were calculated as measures of relative risk. Standardized incidence ratios represent observed events in the study cohort divided by the expected number of events — that is, the number of cases that would be expected to occur if the cohort had the same risk as the general population. The expected numbers of cases of adenocarcinoma and high-grade dysplasia among patients with Barrett's esophagus were calculated as the time at risk multiplied by the population incidence rates, according to sex, age (in 5-year intervals), and calendar time. We constructed Kaplan–Meier curves for the time to the development of adenocarcinoma and for the time to development of adenocarcinoma or high-grade dysplasia according to the presence or absence of low-grade dysplasia at baseline, treating death as a competing risk. Finally, Cox proportional-hazard regression (adjusted for sex, age, and calendar time) was used to calculate hazard ratios as a measure of the relative risks of adenocarcinoma and high-grade dysplasia, according to the presence or absence of low-grade dysplasia at baseline and during follow-up. Low-grade dysplasia was included in the model as a time-dependent variable.

RESULTS

PATIENTS

Of the 11,028 patients with Barrett's esophagus, 7366 were men (66.8%) and 3662 were women (33.2%); the total follow-up time was 67,105 person-years, and the median follow-up time was 5.2 years (interquartile range, 2.8 to 8.9) (Table 1). The median age at baseline was 62.7 years (interquartile range, 52.3 to 73.0).

INCIDENCE OF ADENOCARCINOMA AMONG PATIENTS WITH BARRETT'S ESOPHAGUS

During the follow-up period (1992 through 2009), a total of 197 patients received a new diagnosis of adenocarcinoma, 66 of whom (33.5%) received the diagnosis after the first year of follow-up (Tables 1 and 2). The median age at diagnosis was 68.1 years (interquartile range, 58.5 to 78.3). During the same period, 2602 new esophageal adenocarcinomas were diagnosed in the general population. Thus, the 197 adenocarcinomas diagnosed among all patients known to have Barrett's esophagus nationwide represented 7.6% of all incident adenocarcinomas.

In the study cohort, the overall incidence rate of adenocarcinoma after an initial diagnosis of Barrett's esophagus was 2.9 cases per 1000 person-years (95% confidence interval [CI], 2.6 to 3.4), and the standardized incidence ratio was 29.0 (95% CI, 25.1 to 33.3). After the exclusion of cases diagnosed during the first year of follow-up (131 cases), the incidence of adenocarcinoma was 1.2 cases per 1000 person-years (95% CI, 0.9 to 1.5), and the standardized incidence ratio was 11.3 (95% CI, 8.8 to 14.4) (Table 2 and Fig. 1 and 2). The annual risk was 0.12% (95% CI, 0.09 to 0.15), or 1 case of adenocarcinoma per 860 patient-years.

INCIDENCE OF HIGH-GRADE DYSPLASIA AND OF HIGH-GRADE DYSPLASIA OR ADENOCARCINOMA

A diagnosis of high-grade dysplasia was made in 72 patients (0.7% of patients at risk) during the first year after the index endoscopy and in 106 patients (1.1% of patients at risk) during the subsequent years (Tables 1, 2, and 3). The incidence rate

Table 1. Characteristics of the 11,028 Patients with Barrett's Esophagus.

Characteristic	Total Cohort with Barrett's Esophagus
Sex — no. (%)	
Male	7366 (66.8)
Female	3662 (33.2)
Age at diagnosis of Barrett's esophagus — yr	
Median	62.7
Interquartile range	52.3–73.0
Person-yr at risk	
First yr	67,105
>1 yr	56,782
Follow-up — yr	
Median	5.2
Interquartile range	2.8–8.9
Time to diagnosis of adenocarcinoma — yr	
Median	4.8
Interquartile range	2.5–8.4
Age at diagnosis of adenocarcinoma — yr	
Median	68.1
Interquartile range	58.5–78.3
Time to diagnosis of high-grade dysplasia — yr	
Median	4.7
Interquartile range	2.4–8.3
Age at diagnosis of high-grade dysplasia — yr	
Median	68.0
Interquartile range	58.4–78.3
Total cases of esophageal adenocarcinoma during first yr — no.	131
Total cases of incident esophageal adenocarcinoma after first yr — no.	66
Total cases of high-grade dysplasia during first yr — no.	72
Total cases of incident high-grade dysplasia after first yr — no.	106

of high-grade dysplasia after the first year of follow-up was 1.9 cases per 1000 person-years (95% CI, 1.6 to 2.3). The incidence rate of high-grade dysplasia or adenocarcinoma after the first year of follow-up was 2.6 cases per 1000 person-years (95% CI, 2.2 to 3.1), yielding a standardized incidence ratio for high-grade dysplasia or adenocarcinoma of 21.1 (95% CI, 17.8 to 24.7) among patients with Barrett's esophagus.

LOW-GRADE DYSPLASIA AS A RISK FACTOR

At the time of the diagnosis of Barrett's esophagus, 621 patients (5.6%) had a concurrent diagnosis of low-grade dysplasia. After the first year of follow-up, esophageal adenocarcinomas developed in 52 patients (0.5%) without low-grade dysplasia and in 14 (2.3%) with low-grade dysplasia. The incidence rate among patients without low-grade dysplasia was 1.0 case per 1000 person-years (95% CI, 0.7 to 1.3), and the incidence rate among those with low-grade dysplasia was 5.1 cases per 1000 person-years (95% CI, 3.0 to 8.6). The relative risk of esophageal adenocarcinoma among patients who had low-grade dysplasia at baseline, as compared with those who did not have low-grade dysplasia at baseline, was 4.8 (95% CI, 2.6 to 8.8).

The incidence rate of high-grade dysplasia or adenocarcinoma was markedly increased among patients who had low-grade dysplasia at baseline as compared with patients who did not have low-grade dysplasia at baseline (Tables 2 and 3). The relative risk of high-grade dysplasia was 4.7 (95% CI, 3.0 to 7.6) if patients had low-grade dysplasia at baseline, and the relative risk of high-grade dysplasia or adenocarcinoma was 5.1 (95% CI, 3.4 to 7.6) if patients had low-grade dysplasia at baseline. The incidence rates for patients who had received a diagnosis of low-grade dysplasia during follow-up were as high as those for patients who had low-grade dysplasia at baseline (Tables 2 and 3).

SEX AND AGE AS RISK FACTORS

The incidence rate of adenocarcinoma after the first year of follow-up was 1.5 cases per 1000 years (95% CI, 1.1 to 1.9) among men, as compared with 0.5 cases per 1000 years among women (95% CI, 0.3 to 1.0). The incidence of each end point increased with age and was highest among patients older than 70 years of age (Tables 2 and 3 and Fig. 1).

DISCUSSION

The main finding of our large, population-based study was that the absolute risk of esophageal adenocarcinoma after a diagnosis of Barrett's esophagus was several times lower than the risk reported in previous studies, which forms the basis

Table 2. Incidence of Esophageal Adenocarcinoma and of High-Grade Dysplasia among Patients with Barrett's Esophagus.*

Variable	No. of Events in Study Cohort	No. of Person-Yr of Risk	No. of Expected Events	Incidence Rate/1000 Person-Yr (95% CI)		Standardized Incidence Ratio (95% CI)†
				Study Cohort	General Population	
Adenocarcinoma						
Total cases	66	56,782	5.8	1.2 (0.9–1.5)	0.03 (0.028–0.031)	11.3 (8.8–14.4)
Sex						
Female	10	19,011	0.7	0.5 (0.3–1.0)	0.01 (0.09–0.01)	15.3 (7.3–28.1)
Male	56	37,771	5.2	1.5 (1.1–1.9)	0.048 (0.04–0.05)	10.8 (8.2–14.0)
Age						
30–49 yr	2	9,708	0.1	0.2 (0.05–0.8)	0.0024 (0.002–0.003)	28.3 (3.4–102.2)
50–69 yr	27	26,887	2.1	1.0 (0.7–1.5)	0.051 (0.048–0.054)	13.1 (8.6–19.0)
≥70 yr	37	20,187	3.7	1.8 (1.3–2.5)	0.13 (0.12–0.15)	10.0 (7.1–13.8)
Low-grade dysplasia						
Present on index endoscopy	14	2,741	0.4	5.1 (3.0–8.6)	NA	35.8 (19.6–60.0)
Absent on index endoscopy	52	54,041	5.4	1.0 (0.7–1.3)	NA	9.6 (7.1–12.5)
Occurring at any time during follow-up	23	4,175	0.6	5.5 (3.7–8.3)	NA	40.1 (25.4–60.2)
High-grade dysplasia						
Total cases	106	56,346	1.6	1.9 (1.6–2.3)	0.008 (0.007–0.008)	65.3 (53.5–79.0)
Sex						
Female	23	18,909	0.2	1.2 (0.8–1.8)	0.0038 (0.003–0.004)	97.6 (61.8–146.4)
Male	83	37,437	1.4	2.2 (1.8–2.7)	0.012 (0.011–0.013)	59.9 (47.7–74.2)
Age						
30–49 yr	5	9,700	0.03	0.5 (0.2–1.2)	0.0008 (0.0006–0.001)	155.0 (50.2–361.2)
50–69 yr	62	26,663	0.8	2.3 (1.8–3.0)	0.017 (0.016–0.019)	81.8 (62.7–104.8)
≥70 yr	39	19,983	0.8	2.0 (1.4–2.7)	0.029 (0.026–0.033)	46.9 (33.3–64.0)
Low-grade dysplasia						
Present on index endoscopy	22	2,569	0.1	8.6 (5.6–13.0)	NA	238.0 (149.1–360.4)
Absent on index endoscopy	84	53,777	1.5	1.6 (1.3–1.9)	NA	54.9 (43.8–68.0)
Occurring at any time during follow-up	43	3,835	0.1	11.2 (8.3–15.1)	NA	305.5 (221.1–411.5)

* Events during the first year after the baseline endoscopy were excluded from the calculations. Included are all the cases diagnosed during the period after the first year through year 17 of follow-up (i.e., from 1993 through 2009). NA denotes not available.
† The standardized incidence ratio was calculated as the observed number of events in the cohort with Barrett's esophagus divided by the expected number of events in the general population.

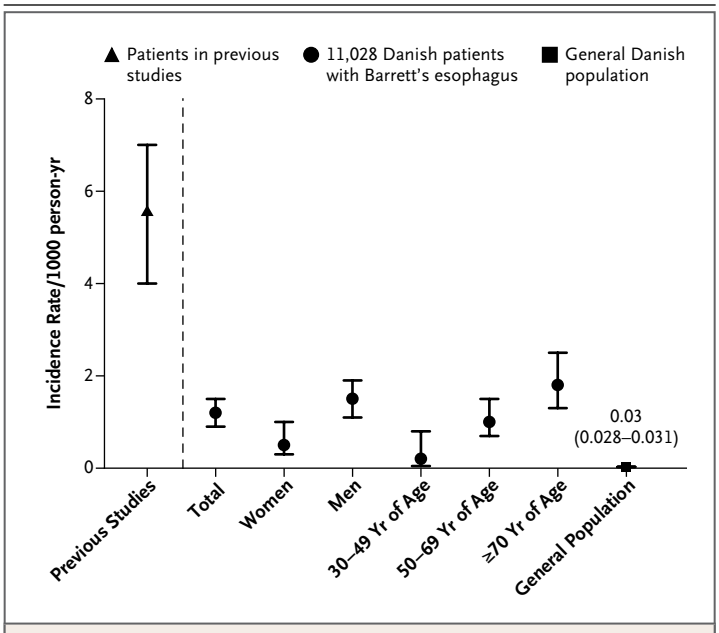

Figure 1. Incidence Rates of Esophageal Adenocarcinoma.

Incidence rates of esophageal adenocarcinoma are shown in a cohort of 11,028 Danish patients with Barrett's esophagus, as compared with mean incidence rates in the Danish general population and with mean incidence rates from previous international studies.[9,17,24,25] I bars indicate 95% confidence intervals.

for current surveillance guidelines.[22,23] The relative risks of adenocarcinoma and high-grade dysplasia in patients with Barrett's esophagus as compared with the general population were high but were also significantly lower than previously reported.[9,24] When low-grade dysplasia was present at the time of the diagnosis of Barrett's esophagus, the absolute and relative risks increased substantially. However, more than two thirds of all adenocarcinomas were diagnosed during the first year of follow-up, probably because the cancer had been overlooked at the time of the diagnosis of Barrett's esophagus or because of a biopsy sampling error on the index endoscopy.

This study is one of the largest follow-up studies to date on the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. It is also one of the few population-based, nationwide studies that involved patients of all ages and both sexes with Barrett's esophagus, with little loss to follow-up. The population-based setting, in which patients received free health care and investigators had access to medical registries, largely eliminated referral and diagnostic bias. The generalizability of our results is therefore high.

Our data extend previous research in several ways. During the past decade, the risk of adenocarcinoma in patients with Barrett's esophagus has been estimated in several studies, most of which involved only a few hundred patients, thus increasing the risk of publication bias.[14,16,19,24,32] Four reviews[9,17,24,25] have attempted to overcome these limitations by pooling incidence rates from U.S. and European studies. The overall incidence rates of adenocarcinoma in the four reviews ranged from 5.3 to 7.0 cases per 1000 person-years. There was a tendency toward higher incidence rates in smaller studies and lower rates in European studies.

Two previous registry studies with a design similar to ours but with different types of registries, fewer patients, and shorter follow-up periods showed incidence rates of 4.0 and 5.0 cases per 1000 person-years[26,27] — rates that were 4 and 5 times as high, respectively, as the incidence rate in the current study. In another registry study, the incidence of high-grade dysplasia or adenocarcinoma was estimated to be 1.1% per year.[28] However, these studies were limited by selected patient samples and by loss to follow-up or exclusion of many of the original cohort patients with Barrett's esophagus, thus possibly biasing the reported incidence and making generalization to other populations difficult. In a recent study from the Netherlands,[29] the incidence rate of adenocarcinoma among patients who underwent follow-up endoscopic examinations was calculated to be 4.3 cases per 1000 person-years, and the incidence rate of high-grade dysplasia or adenocarcinoma was calculated to be 5.8 cases per 1000 person-years. The study did not include a comparison with data from the general population, and the incidence rate reported for patients with no follow-up endoscopic examination was substantially lower, indicating that the patients who underwent follow-up endoscopic examinations might have been a selected high-risk group.

The results of our population-based study are largely consistent with those of a recent study from Northern Ireland,[30] in which the incidence rate of adenocarcinoma (excluding cases that were diagnosed during the first year) was reported to be 1.3 cases per 1000 patient-years, and the incidence rate of high-grade dysplasia or adenocarcinoma was reported to be 2.2 cases per 1000 patient-years. Low-grade dysplasia at baseline was also a strong risk factor in that study, with inci-

dence rates of 9.2 cases of adenocarcinoma per 1000 patient-years and 14.0 cases of high-grade dysplasia or adenocarcinoma per 1000 patient-years among patients with low-grade dysplasia at baseline. No estimates of relative risk were available. A recent study in which Markov models were used to evaluate available data on the incidence of adenocarcinoma supports our findings, highlighting the very low incidence among women in all age groups and among men younger than 50 years of age and suggesting that surveillance is not beneficial.[31]

Our study also has some methodologic factors that might affect the accuracy of our estimates. First, in this registry-based study, patients were not subject to a protocol that was as strict as that in prospective studies. Second, heightened awareness among clinicians and pathologists increased the number of cases of Barrett's esophagus diagnosed throughout the study period. Third, during the final years of the study, classification of moderate dysplasia was merged with the existing classification of low-grade dysplasia and high-grade dysplasia. In our estimates, the patients with moderate dysplasia were merged with those with high-grade dysplasia. However, the number of patients with moderate dysplasia in our cohort was small, and when we merged these patients with those with low-grade dysplasia instead, the incidence rates differed only slightly.

Fourth, the challenges of and developments in pathological classification make it difficult to carry out an accurate, large, epidemiologic follow-up study in which patients are stratified according to the level of dysplasia.[28,32] The clinical course of the development of adenocarcinoma in patients with Barrett's esophagus is thought to progress through stages of low-grade dysplasia and high-grade dysplasia — a process that spans several years. The diagnosis of the various stages is dependent on the site of the biopsy, making it difficult to ascertain the transition time from Barrett's esophagus to low-grade dysplasia or high-grade dysplasia.[33] Earlier studies have shown that among patients in whom low-grade dysplasia had previously been diagnosed, only 25 to 30% retained the diagnosis on follow-up endoscopy, owing to sampling errors, disagreements on classification, or a true reversion of dysplasia.[14,34-36]

In several studies, patients in whom low-grade dysplasia was detected on the first endoscopy or during follow-up have been shown to be at increased risk for high-grade dysplasia or adenocarcinoma.[22,28,34,35,37] We therefore also calculated the risk of high-grade dysplasia or adenocarcinoma in an analysis that included patients with low-grade dysplasia at baseline and in a separate analysis that included patients who had received a diagnosis of low-grade dysplasia at any time during follow-up. Owing to the difficulties involved in precisely reconfirming dysplasia on follow-up endoscopy, as described above, patients remained in the low-grade-dysplasia group whether or not such dysplasia was found on later endoscopic examinations.

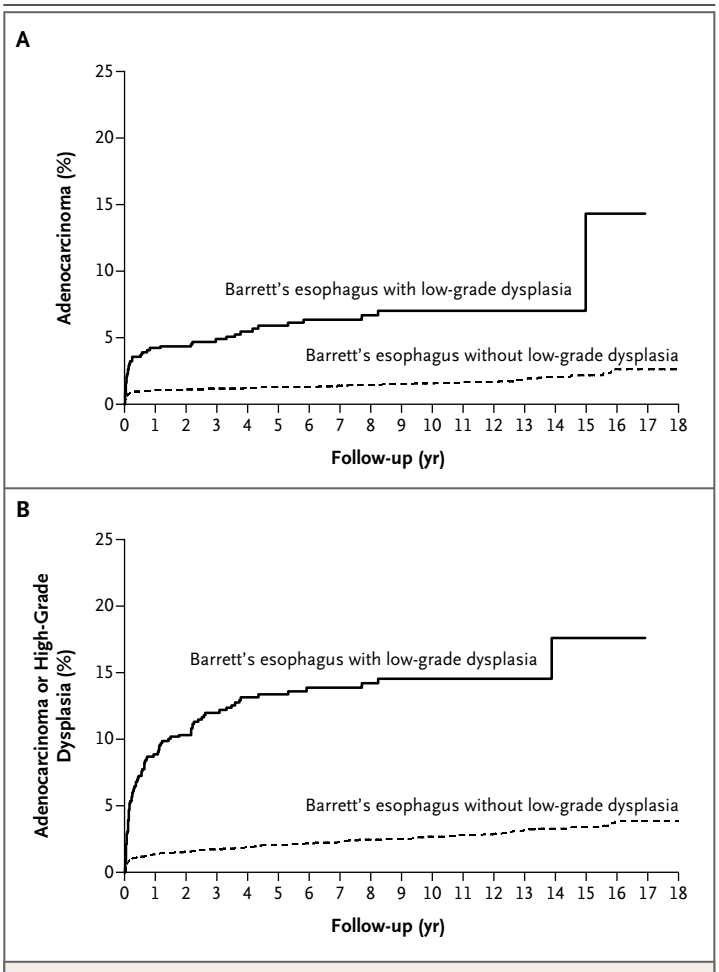

Figure 2. Cumulative Incidence of Esophageal Adenocarcinoma and of Esophageal Adenocarcinoma or High-Grade Dysplasia.

Shown is the cumulative incidence of esophageal adenocarcinoma (Panel A) and of esophageal adenocarcinoma or high-grade dysplasia (Panel B) among patients with Barrett's esophagus, according to the presence or absence of low-grade dysplasia on baseline endoscopy. Kaplan–Meier plots include data from the first year after the index endoscopy.

Table 3. Incidence of High-Grade Dysplasia or Esophageal Adenocarcinoma in Patients with Barrett's Esophagus.*

Variable	No. of Cases of High-Grade Dysplasia or Adenocarcinoma in Study Cohort	Person-Yr of Risk	No. of Expected Cases	Incidence Rate/1000 Person-Yr (95% CI)		Standardized Incidence Ratio (95% CI)†
				Study Cohort	General Population	
Total cases	148	56,151	7.0	2.6 (2.2–3.1)	0.035 (0.034–0.036)	21.1 (17.8–24.7)
Sex						
Female	29	18,891	0.9	1.5 (1.1–2.2)	0.015 (0.014–0.016)	33.9 (22.7–48.7)
Male	119	37,260	6.2	3.2 (2.7–3.8)	0.056 (0.054–0.058)	19.3 (16.0–23.1)
Age						
30–49 yr	7	9,696	0.1	0.7 (0.3–1.5)	0.0031 (0.0027–0.0036)	71.6 (28.7–147.6)
50–69 yr	76	26,561	2.6	2.9 (2.3–3.6)	0.065 (0.062–0.069)	28.7 (22.6–36.0)
≥70 yr	65	19,894	4.3	3.3 (2.6–4.2)	0.16 (0.15–0.17)	15.2 (11.7–19.3)
Low-grade dysplasia						
Present on index endoscopy	32	2,525	0.4	12.7 (9.0–17.9)	NA	75.9 (51.9–107.2)
Absent on index endoscopy	116	53,625	6.6	2.2 (1.8–2.6)	NA	17.6 (14.5–21.1)
Occurring at any time during follow-up	55	3,760	0.6	14.6 (11.2–19.1)	NA	89.0 (67.0–115.8)

* Events during the first year after the endoscopy were excluded from the calculations. Included are all the cases diagnosed during the period after the first year through year 17 of follow-up (i.e., from 1993 through 2009). NA denotes not available.

† The standardized incidence ratio was calculated as the observed number of events in the cohort with Barrett's esophagus divided by the expected number of events in the general population.

Fifth, our main focus was on all new cancers that developed more than 1 year after the diagnosis of Barrett's esophagus. Not all similar studies have excluded the cases of adenocarcinomas detected within the first year after a diagnosis of Barrett's esophagus but instead have included all cases. However, in most of the more recent reviews and studies, the cases detected during the first year were excluded from calculations of the incidence rates, as they were in our study.[9,17,30] To extend the possibility of comparison, we also provide an overall incidence rate that includes cases diagnosed during the first year.

Finally, in most countries, including Denmark, the criterion for the diagnosis of Barrett's esophagus is the presence of specialized intestinal metaplasia — that is, intestinal metaplasia with goblet cells as part of a columnar-lined esophagus. However, several studies have shown that the risk of dysplasia or adenocarcinoma is not necessarily related to the presence or absence of goblet cells, because the detection of these cells is strongly associated with the number of biopsy specimens obtained.[30,38] Therefore, future classifications of Barrett's esophagus might not require the presence of goblet cells, which would increase the number of patients considered to be at risk.

In conclusion, in this large, nationwide, population-based study, we found that the incidence of esophageal adenocarcinoma among patients with Barrett's esophagus, with or without low-grade dysplasia, was 4 to 5 times lower than that previously reported. The relative risk of adenocarcinoma, which was 11 times as high among patients with Barrett's esophagus as it was in the general population, was significantly lower than that in earlier studies.[9,24] Our study provides solid evidence that esophageal adenocarcinoma will develop in very few patients with Barrett's esophagus. Together with another recent study,[30] as well as studies of cost-effectiveness and patients' quality of life, the results of our study suggest that the risk of esophageal adenocarcinoma among patients with Barrett's esophagus is so minor that in the absence of dysplasia, routine surveillance of such patients is of doubtful value.[9,39-41]

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No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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