Risk of Mortality and Cancer Incidence in Barrett's Esophagus

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Abstract

Background: **There are very few prospective follow-up studies of Barrett esophagus (BE) cohorts assessing the risk of extraesophageal cancer incidence or mortality. Such studies are necessary in order to understand the overall risks of cancer and death experienced by patients with BE.**

Methods: **A cohort of 502 patients with BE were identified at Leeds General Infirmary, England. Mortality and cancer incidence information were provided by the Office for National Statistics. Standardized mortality ratios (SMR) and standardized incidence ratios (SIR) were calculated using indirect standardization.**

Results: **All-cause mortality was found to be elevated in patients with BE [SMR, 1.21; 95% confidence interval (95% CI), 1.06, 1.37] and remained so after esophageal cancers were excluded (SMR, 1.16; 95% CI, 1.01-1.32). Increased mortality risks were also found for malignant neoplasms of the esophagus (SMR, 7.26; 95% CI, 3.87-12.42) and diseases of the digestive system (SMR, 2.03; 95% CI, 1.11-3.40). The remaining disease categories produced no altered risk estimates. Circulatory disease mortality was borderline statistically significant (SMR, 1.24; 95% CI, 1.00-1.52; $P = 0.053$) for those with a specialized intestinal metaplasia diagnosis of BE. In the cancer incidence analyses, esophageal malignancies (SIR, 8.66; 95% CI, 4.73-14.53) and esophageal adenocarcinomas (SIR, 14.29; 95% CI, 7.13-22.56) were found to be increased in BE. All remaining analyses provided unaltered risks, including that of colorectal cancer.**

Conclusions: **This study has shown evidence of an increased risk of esophageal cancer incidence and mortality in BE. It has also shown that those who have a histologic BE diagnosis may also have an increased risk of circulatory disease mortality.** (Cancer Epidemiol Biomarkers Prev 2007;16(10):2090–6)

Introduction

Barrett's esophagus (BE) describes a columnar-lined metaplasia of the lower esophagus characterized by goblet cells (1), the predominant risk factor for which is gastroesophageal reflux disease (2). BE is of importance due to the increased risk it confers for esophageal adenocarcinoma (EA) of approximately 10 to 55 times that of the general population (3-8). The observed and unexplained increasing incidence has augmented interest in this precancerous lesion (9-11). This has prioritized the importance of understanding the risks of disease and mortality attributable to BE. Identifying these risks, with regard to the clinically diagnosed BE population, may offer the opportunity to provide preventative interventions, thereby reducing disease burden and associated economic costs.

There have been few studies which have investigated specific causes of mortality or extraesophageal cancer incidence in BE. Regarding risk of death in BE, most studies have only analyzed all-cause mortality. Of these, three studies found no altered risk (12-14), whereas two later studies, which were updated analyses of two of the previously cited studies, reported an increased overall risk of death [$P = 0.0006$; ref. 8; standardized mortality ratio (SMR), 1.46; 95% confidence interval (95% CI): 1.16, 1.82; ref. 6]. Two additional studies have been published recently (15, 16). The study by Solaymani-Dodaran et al. (16) provides risk estimates from a BE cohort identified from the U.K. General Practice Research Database and the results show that patients with BE have an increased risk of death from esophageal cancer (attributable risk = 4.41/1,000 patient years) and death from all causes excluding esophageal cancer mortality (hazard ratio, 1.37; 95% CI, 1.12-1.66), the latter of which is proposed to be the result of an increased risk for cardiovascular disease. Anderson et al. (15) report results from an Irish cohort of patients with BE. Mortality from EA (SMR, 5.18; 95% CI, 2.25-8.12) and diseases of the digestive system (SMR, 2.11; 95% CI, 1.11-3.11) were both significantly increased, whereas cerebrovascular disease mortality (SMR, 0.65; 95% CI, 0.37-0.93) was significantly reduced.

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Although the increased standardized incidence ratio (SIR) for EA has been clearly established, it has also been suggested that BE may increase the risk of extraesophageal malignancies. An association of BE with colorectal cancer has been reported (odds ratio, 5.19; 95% CI, 2.35-11.92; ref. 17), although evidence for such a relationship has been inconsistent (18, 19).

This study compares the mortality and cancer incidence of a BE cohort, recruited at Leeds General Infirmary, to the general population of West Yorkshire. This study is the first to undertake both a thorough and robust mortality and cancer incidence analysis of a BE cohort.

Materials and Methods

The Leeds General Infirmary BE cohort is composed of all patients with an index diagnosis of BE between January 31, 1984 and January 31, 1995 (20). BE was defined as the histologic diagnosis of columnar-lined esophagus (CLE) of at least 3 cm in length above the endoscopically determined gastroesophageal junction or the presence of specialized intestinal metaplasia (SIM) anywhere within the esophagus. Analyses were conducted which (*a*) included all patients with BE (SIM and CLE) and (*b*) just included those with a SIM diagnosis of BE (SIM).

The distinction between these diagnostic methods is important as SIM is the *sine qua non* of BE. Historically, this has not been the case; rather, a certain length of CLE was sufficient for diagnosis, and this was most often set at 3 cm, as used for this cohort (20). The absence of SIM information for those with a diagnosis of CLE was the motivation for an analysis of the data excluding this group, a strategy also used by a previous study (15).

In the original study cohort, there were a total of 626 patients with BE. From this cohort, exclusions were made of individuals who had a cancer diagnosis (excluding nonmelanoma skin cancer, NMSC) prior to or within 6 months of their BE diagnosis or were <18 years of age at BE diagnosis.

Ethical approval was given by Leeds West Research Ethics Committee, whereas the Patient Information Advisory Group granted Section 60 support [4-08(h)/2004] on behalf of the Department of Health. Variables required for the identification of patients on the National Health Service Central Register, held by the Office for National Statistics, were extracted from electronic and hardcopy patient notes and the National Health Service Strategic Tracing Service. These included surname, forename, sex, National Health Service number, date of birth, address(es), address dates, date of death, other initials, other surname, alternative address, alternative address date, and alternative date of birth. Subsequent to submission of these data, the Office for National Statistics approved the study and attempted to identify patients on the provided variables both automatically and then manually. They were then able to send mortality and cancer incidence event data for those members of the cohort who were successfully identified.

For calculation of SMRs and SIRs, mortality and cancer incidence rates for the population of West Yorkshire were used to estimate the number of expected deaths/cases. West Yorkshire is the county within which Leeds is the largest city. The population size of West Yorkshire was stable at 2 million between 1985 and 1995,[4] while population migration has also been fairly stable, as it has been for the majority of England and Wales (21). In 1991, the predominant ethnic group in West Yorkshire was White (92%), followed by Pakistani (4%), Indian (1.7%), and then Black (1.2%). Mortality data for the West Yorkshire population were provided by Office for National Statistics, for the period 1980 to 2003 stratified by sex and 10-year age bands, whereas cancer incidence data were provided by the Northern and Yorkshire Cancer Registry and Information Service, for the period 1980 to 2004 stratified by sex and 5-year age bands. Therefore, the SMR and SIR analyses were bound to these periods and stratifications. West Yorkshire population figures for the corresponding time period were also provided by the Office for National Statistics and these allowed rates of mortality and cancer incidence to be calculated per person-year. For calculation of the expected numbers of events, quinquennial population rates were used. STATA 8.2 (22) and the commands stset, stptime and smri were used for analysis.

Results

Prior to any exclusions, there were 626 patients with BE in the original cohort (20). Those excluded were 17 patients who failed to meet the diagnostic criteria, 15 who lacked clinical records, 11 who had a diagnosis of BE before January 31, 1984, 4 who were <18 years of age, and 1 who died on the same day as their diagnostic endoscopy. Those lost due to follow-up included 8 who could not be traced by the Office for National Statistics, 41 who had a cancer diagnosis previous to their BE diagnosis, and 27 who had a cancer diagnosis within the first 6 months of their BE diagnosis. The latter 27 cancers included 17 esophageal (all adenocarcinomas; C15), 1 stomach (C16), 4 colorectal (C18-C20), 1 pancreas (C25), 1 lung (C34), 1 prostate (C61), 1 Hodgkin's disease (C81), and 1 multiple myeloma (C90).

Of the 502 patients with BE which remained for analysis, 431 had a BE diagnosis of SIM and 71 had a diagnosis of CLE. Table 1 outlines the summary statistics for the full BE cohort (SIM and CLE) and the SIM group alone.

In this table, follow-up for the mortality and cancer incidence analyses was not the same due to the years of comparison data available and use of different failure criteria. Comparison data for the mortality analysis allowed follow-up for the period January 31, 1984 to December 31, 2004, whereas failure was date of death. Due to the unavailability of comparison data for 2004, the cancer incidence analysis constituted the period January 31, 1984 to December 31, 2003, whereas failure was first malignant cancer diagnosis (excluding NMSC). Each SMR and SIR analysis was conducted for all patients with BE and the SIM group alone, the results of which did not differ. Therefore, results presented in Tables 2 and Table 3 are of the full BE cohort (SIM and CLE) and it is these results that are discussed unless otherwise specified. The results of the mortality and cancer incidence analyses of the SIM BE group which were, or

[4] Office for National Statistics data, personal communication, 2006.

Table 1. Characteristics of cohort for cancer incidence and mortality analysis

	SIM and CLE (SD)		SIM (SD)	
	Males	Females	Males	Females
No. of patients (*n*)	274	228	239	192
Average age at BE diagnosis	58.8 (14.6)	68.7 (12.3)	59.5 (13.9)	69.0 (12.1)
Total no. of patients (*N*)	502		431	
Mortality analysis				
Total follow-up (y)	5,247		4,406	
Average follow-up (y)	10.5 (5.0)		10.2 (5.0)	
No. of mortalities	246		209	
Cancer incidence analysis				
Total follow-up	4,802		4,021	
Average follow-up	9.6 (4.8)		9.4 (4.8)	
No. of cancer incidences	72		65	

approached the threshold of being, statistically significant are presented in Table 4.

It is important to note that the death certificates do not provide histologic information of malignancies and so the neoplastic mortality analyses are site-specific only (e.g., esophageal cancer). In contrast, cancer registrations do provide histologic information and so different histologies may be grouped (e.g., esophageal cancer) or analyzed separately (e.g., esophageal adenocarcinoma).

Table 2 shows that all-cause mortality was significantly elevated in patients with BE (SMR, 1.21; 95% CI, 1.06-1.37; $P < 0.01$) and remained so after deaths from esophageal cancer were excluded (SMR, 1.16; 95% CI, 1.01-1.32; $P < 0.05$). For neoplastic mortality, the only cancer site category that had a statistically significant altered risk estimate was esophageal cancer (SMR, 7.26; 95% CI, 3.87-12.42; $P < 0.001$). All other site-specific cancer mortality analyses, including that for colorectal cancer, were consistent with the null hypothesis. For nonneoplastic mortality, an increased risk for diseases of the digestive system was found in patients with BE (SMR, 2.03; 95% CI, 1.11-3.40; $P < 0.05$). Circulatory disease mortality was statistically nonsignificant for the SIM and CLE group combined but was of borderline statistical significance for the SIM group alone (SMR, 1.24; 95% CI, 1.00-1.52; $P = 0.053$). The remaining mortality analyses, including various circulatory diseases, were all statistically nonsignificant.

Table 3 shows the SIR results. For all malignant neoplasms combined (excluding NMSCs) the SIR was 1.12 (95% CI, 0.88-1.41), which decreased and remained statistically nonsignificant when esophageal cancer was excluded (SIR, 0.93; 95% CI, 0.70-1.20). The SIRs for esophageal malignancy were statistically significant for both the analysis of the full BE cohort (SIR, 8.66; 95% CI, 4.73-14.53; $P < 0.001$) and the SIM group alone (SIR, 10.09; 95% CI, 5.52-16.94; $P < 0.001$), whereas the EA analyses produced higher SIRs of 14.29 (95% CI, 7.13-22.56; $P < 0.001$) for the full BE cohort analysis and 16.42 (95% CI, 8.20-29.38; $P < 0.001$) for the SIM group alone. The EA analyses were repeated with the addition of three other patients with esophageal cancer in which

Table 2. Results of SMR analyses for the BE cohort

Underlying cause of death (ICD-10 code)	Observed	Expected	SMR (95% CI)
All causes (A00-R99, V01-Y89)	246	203.06	1.21* (1.06-1.37)
All causes (A00-R99, V01-Y89) excluding esophageal malignancy (C15)	233	201.27	1.16† (1.01-1.32)
Neoplastic mortality			
All neoplasms (C00-D48)	54	47.63	1.13 (0.85-1.48)
All neoplasms excluding esophageal cancer (C00-C14, C16-D48)	41	45.84	0.89 (0.64-1.21)
Malignant neoplasm of esophagus (C15)	13	1.79	7.26‡ (3.87-12.42)
Malignant neoplasm of stomach (C16)	3	2.71	1.11 (0.23-3.24)
Malignant neoplasm of trachea, bronchus, and lung (C33-C34)	14	12.36	1.13 (0.62-1.90)
Malignant neoplasm of colon, rectosigmoid junction, and anus (C18-C21)	2	5.09	0.39 (0.05-1.42)
Nonneoplastic mortality			
Diseases of the circulatory system (I00-I99)	101	89.40	1.13 (0.92-1.37)
Acute myocardial infarction (I21-I22)	34	29.59	1.15 (0.80-1.61)
Ischemic heart disease excluding myocardial infarction (I23-I25)	25	20.50	1.22 (0.79-1.80)
Cerebrovascular disease (I60-I69)	22	23.73	0.93 (0.58-1.40)
Diseases of the respiratory system (J00-J99)	40	33.27	1.20 (0.86-1.64)
Diseases of the digestive system (K00-K93)	14	6.92	2.03† (1.11-3.40)

NOTE: 95% CIs are Poisson exact. The underlying causes of death and ICD-10 codes for individuals only included in the ''All-cause'' categories of analysis include septicemia (A412), aplastic anemia (D619), diabetes mellitus (E149; $n = 2$), mental and behavioral disorders (F03, $n = 3$; F102), diseases of the nervous system (G20, G309, G409), diseases of the musculoskeletal system and connective tissue (M009, $n = 2$; M259, M809), diseases of the genitourinary system (N179, N19, N390; $n = 2$), senility (R54, $n = 7$), motor vehicle accident, traffic (V892), fall on and from stairs and steps (W100, $n = 2$), accidental alcohol poisoning (X450, $n = 2$), exposure to unspecified factor causing injury (X598, X599), external cause, undetermined intent (Y120, Y219), surgical procedure (Y833, Y839). These deaths were not analyzed in a specific category due to limited numbers or irrelevant causes (i.e., R54, senility).

*Twice, one-sided $P < 0.01$.

† Twice, one-sided $P < 0.05$.

‡ Twice, one-sided $P < 0.001$.

Table 3. Results of SIR analyses for the BE cohort

Cancer incidence (ICD-10 code)	Observed	Expected	SIR (95% CI)
All malignant neoplasms (C00-C97) excluding NMSCs (C44)	72	64.14	1.12 (0.88-1.41)
All malignant neoplasms (C00-C97) excluding NMSCs (C44) and esophageal malignancy (C15)	58	62.53	0.93 (0.70-1.20)
Malignant neoplasm of digestive organs (C15-C26)	32	17.23	1.86* (1.27-2.62)
Malignant neoplasm of digestive organs excluding esophagus (C16-C26)	18	15.61	1.15 (0.68-1.82)
Malignant neoplasm of esophagus (C15)	14	1.62	8.66† (4.73-14.53)
Malignant neoplasm of esophagus (C15) and stomach (C16)	21	5.05	4.16† (2.57-6.37)
Esophageal adenocarcinoma (C15:81403)	11	0.77	14.29† (7.13-22.56)
Esophageal adenocarcinoma (C15:81403+80103) ‡	14	0.77	18.18† (9.94-30.51)
Malignant neoplasm of colon, rectosigmoid junction and anus (C18-C21)	8	9.21	0.87 (0.38-1.71)
Malignant neoplasm of trachea, bronchus and lung (C33-C34)	14	12.34	1.13 (0.62-1.90)

NOTE: 95% CIs are Poisson exact. Incidence cancers and ICD-10 codes for individuals only included in the ''All-malignant'' categories of analysis include malignant neoplasms of connective and soft tissue (C498), breast (C509, $n = 2$), corpus uteri (C541, C549; $n = 2$), prostate (C61; $n = 6$), kidney (C64), eye, brain, and other parts of the central nervous system (C699, C713, C73), ill-defined, secondary, and unspecified sites (C785, C787; $n = 2$, C792, C793, C80; $n = 2$), lymphoid, hematopoietic and related tissue (C833, C900; $n = 2$). These cancers were not analyzed in a specific category due to limited numbers.
*Twice, one-sided $P < 0.01$.
† Twice, one-sided $P < 0.001$.
‡ Histology 80103 (carcinoma) is assumed to be adenocarcinoma (81403) in this analysis.

there was no histologic information. The resulting SIRs were 18.18 (95% CI, 9.94-30.51; $P < 0.001$) for the full BE cohort and 20.90 (95% CI, 11.42-35.06; $P < 0.001$) for the SIM group alone. In addition, an analysis of esophageal and stomach cancers combined was conducted in order to include any junctional cancers that may have been assigned as gastric rather than esophageal cancer. This estimate was also statistically significant (SIR, 4.16; 95% CI, 2.57-6.37; $P < 0.001$). Although the analysis of digestive disease malignancies was statistically significant, this became nonsignificant when esophageal malignancies were excluded. Neither the SIR for colorectal cancer nor the SIR for other specific types of cancer were statistically significant (see Table 3).

Discussion

This analysis provides point estimates of risk for specific cancer incidence and mortality in a well-defined BE cohort. The average years of follow-up per patient are appreciable and this has allowed for a large proportion of deaths and cancer incidences to accrue. The study design enabled all patients with BE diagnosed over a 10-year period at a single institute to be recruited into the cohort. This methodology precluded several biases inherent to most other published prospective studies of BE, specifically biases resulting from incomplete and selective participation.

The sex ratio of this BE cohort was surprisingly low at 1.2:1 males to females (Table 1), especially when compared with a recent meta-analysis which found a sex ratio of 1.96:1 males to females (95% CI, 1.77-2.17; ref. 23). The reasons for this are unknown but the difference is less pronounced when compared with the BE sex ratio for the U.K. of 1.54:1 males to females (95% CI, 1.37-1.73; ref. 23).

The finding of an increased risk of all-cause mortality (SMR, 1.21; 95% CI, 1.06-1.37) among patients with BE is in agreement with the evidence from the Solaymani-Dodaran study (hazard ratio, 1.37; 95% CI, 1.12-1.66; ref. 16). It contrasts, however, with the only other

Table 4. Summary of relevant results of SMR and SIR analyses for the 431 patients with BE diagnosed with SIM

	Observed	Expected	SMR (95% CI)
Underlying cause of death (ICD-10 code)			
All causes (A00-R99,V01-Y89)	209	169.38	1.23* (1.07-1.41)
All causes (A00-R99,V01-Y89) excluding esophageal malignancy (C15)	197	167.85	1.17† (1.02-1.35)
Neoplastic mortality			
Malignant neoplasm of esophagus (C15)	12	1.54	7.79‡ (4.03-13.61)
Nonneoplastic mortality			
Diseases of the circulatory system (I00-I99)	92	74.40	1.24 (1.00-1.52)
Diseases of the digestive system (K00-K93)	12	5.76	2.08† (1.08-3.64)
Cancer incidence (ICD-10 code)			
Malignant neoplasm of digestive organs (C15-C26)	28	14.71	1.90* (1.26-2.75)
Malignant neoplasm of esophagus (C15)	14	1.39	10.09‡ (5.52-16.94)
Malignant neoplasm of esophagus (C15) and stomach (C16)	19	4.31	4.41‡ (2.65-6.88)
Esophageal adenocarcinoma (C15:81403)	11	0.67	16.42‡ (8.20-29.38)
Esophageal adenocarcinoma (C15:81403+80103)§	14	0.67	20.90‡ (11.42-35.06)

NOTE: 95% CIs are Poisson exact.
*Twice, one-sided $P < 0.01$.
† Twice, one-sided $P < 0.05$.
‡ Twice, one-sided $P < 0.001$.
§Histology 80103 (carcinoma) is assumed to be adenocarcinoma (81403) in this analysis.

comprehensive mortality study (SMR, 0.96; 95% CI, 0.84-1.07; ref. 15). Why the latter BE population in Ireland exhibited no additional overall mortality risk is unclear, but seems to be the net effect of the excesses of risk, mainly for esophageal cancer, and a decreased risk of cerebrovascular disease, both of which are discussed further below.

For the neoplastic mortality analyses, only the esophageal cancer SMR was statistically significant (SMR, 7.26; 95% CI, 3.87-12.42). The estimate is slightly higher but consistent with the Anderson study (SMR, 5.18; 95% CI, 2.25-8.12; ref. 15) and is in agreement, although it cannot be directly compared, with the attributable risk provided in the Solaymani-Dodaran study (4.41/1,000 patient-years; ref. 16).

In a review of 10 BE series, Conio et al. (24) estimated that the average proportion of deaths from EA among patients with BE was 5.3%. In our study, 13 out of 246 deaths were from EA, producing an identical percentage (5.3%) and this increased only slightly (to 5.7%) in the SIM group alone. Therefore, although mortality from this cancer is still relatively low in BE populations, the SMRs show that the risk is still substantially elevated in comparison to the general population.

It should be noted that 4 of the 13 esophageal cancer deaths did not have an incident esophageal cancer registration. Two of these individuals did have an incident cardia cancer registration and it is likely that these cancers traversed the gastroesophageal junction, leading to an incorrect registration of either cancer or death. Due to the uncertainty as to which was incorrect, details for both registrations remained unchanged for analysis. Analysis of both esophageal and stomach (cardia) malignancies combined gave a SIR of 4.16 (95% CI, 2.57-6.37). The two other patients, who had an underlying cause of death of esophageal cancer but no incident registration of any cancer, were assumed to have had an incident esophageal cancer (only for the purposes of a sensitivity analysis), using date of death as a proxy for date of diagnosis. The SIR from this analysis was 20.78 (95% CI, 11.88-33.74). Owing to the fact that this estimate includes inferred cancer incidences, it was not included in the results table.

The SMR estimate for diseases of the digestive system in patients with BE was the only analysis of nonneoplastic mortality to be significantly altered, and this increase in risk is in agreement with the estimate derived from the Irish cohort study (15). Five of the deaths in the SMR analysis for diseases of the digestive system were from causes known to be associated with excessive alcohol consumption (alcoholic cirrhosis, K70.3; alcoholic liver disease, K70.9; cirrhosis of the liver, K74.6, $n = 2$; acute pancreatitis, K85.0) whereas the remaining 9 were not [esophageal ulceration (K22.1), esophageal stricture (K22.2), gastric outflow obstruction (K31.1), unspecified disease of the stomach and duodenum (K31.8), hiatus hernia (K44.9), bowel infection (K52.9), perforated diverticular disease (K57.8), paracolic abscess (K63.0), and gastrointestinal bleeding (K92.2)]. The necessary data to be able to test the hypothesis that patients with BE generally have an increased exposure to alcohol was not available, although there is evidence that this exposure is a risk factor for BE, possibly mediated through an increased risk for gastroesophageal reflux disease (25). Alternatively, there is the possibility that the excess risk represents a selection bias; the diagnosis of BE, in many of these patients, may have been incidental, whereas their original reason for endoscopic referral may have pertained to symptoms of their eventual cause of death.

In the Irish BE cohort (15), a decrease in the risk for cerebrovascular disease was found (SMR, 0.65; 95% CI, 0.37-0.93; $P < 0.05$). This association was not replicated in our study. If the Irish estimate were true, the current study would have 76% power to detect a similar effect at the 0.05 level of significance (26). The reason for this difference is not obvious but could be due to a difference in exposures between the Irish and English populations.

Although the SMR analysis for diseases of the circulatory system was not significantly elevated, the estimate for the SIM group alone was on the borderline of statistical significance in the current study. The causes of excess deaths seemed to be myocardial infarction and ischemic heart disease. There is some earlier evidence to suggest that patients with BE are at an increased risk of circulatory disease. In their study of U.K. data, Solaymani-Dodaran et al. (16) suggested that patients with BE may have an increased risk of ischemic heart disease. This conclusion was reached due to the all-cause mortality hazard ratio losing its statistical significance when ischemic heart disease was added to the multivariable model. Jankowski and Moayyedi (27) have proposed that 42% of patients with BE die from vascular disease relative to 32% of an age- and sex-matched U.K. population. This gives an odds ratio of 1.31 which, if true, would provide this investigation with 86% power to detect a similar change. The underlying link between the association of myocardial ischemia and BE has been postulated to be gastroesophageal reflux disease (28). Alternatively, the association may be mediated by other shared risk factors. In accordance with this argument is evidence that BE populations are less healthy than the general population, when measured by a validated health-related quality of life questionnaire (29), and may thus have an increased risk for other specific comorbidities. Of relevance is evidence that hypertension is associated with both BE (odds ratio, 5.1; 95% CI, 2.5-10.0; ref. 30) and adenocarcinoma of the esophagus and gastric cardia (odds ratio, 2.4; 95% CI, 1.1-5.1; ref. 31). In summary, if there is a real association between circulatory disease and BE, then the evidence would suggest that the risk is modest, whereas the mechanism of association is potentially mediated through excessive adiposity and/or gastroesophageal reflux disease.

Overall, many of the SMR estimates were higher than 1 and, in combination, this provided for an excess in all-cause mortality excluding esophageal cancer. However, if the individuals who died from digestive diseases were also excluded, on the assumption that this excess was due to selection bias, then the point estimate for all remaining causes of death becomes nonsignificant (SMR, 1.13; 95% CI, 0.98-1.29). This assumption, however, may not hold and patients with BE may be at a slightly increased risk of extraesophageal mortality either from circulatory disease or from a variety of nonspecific disorders promoted by an ''unhealthy cohort'' effect.

For cancer incidence other than esophageal malignancies, the analysis of all malignant neoplasms excluding

NMSCs was not statistically significant and concurs with the only other result considering extraesophageal malignancies (hazard ratio, 1.14; 95% CI, 0.80-1.64; ref. 18). A statistically significant increased SIR was found for malignant neoplasm of digestive organs, but this became nonsignificant once esophageal malignancies were excluded, thus confirming that the only increased malignant risk of BE is that for EA.

Esophageal malignancy was expected to be increased in patients with BE due to the weight of the evidence set out in the Introduction. In this analysis, the SIR for all esophageal malignancies was 8.66 (95% CI, 4.73-14.53; $P < 0.001$). The most valuable estimates of risk for comparison are those provided by Conio et al. (SIR, 10.5; 95% CI, 7-14; ref. 8) and Solaymani-Dodaran et al. (SIR, 9.8; 95% CI, 4-22; ref. 3). The former is reported from an almost completely SIM diagnosed cohort, whereas the latter is representative of the U.K. In addition, both of these studies were relatively large, the first having observed four EAs in 585 person-years of follow-up (8), whereas the second identified 13 EAs in 2,615 person-years (3). In addition, both of these studies were explicit in their use of the correct SIR methodology, having stratified by both age and sex in their calculation of a denominator.

For calculation of an upper estimate, three histologically undefined esophageal cancers were assumed to be adenocarcinomas (Table 3). This assumption is reasonable given the increased risk for EA which BE presents. The most informative estimate, however, is probably that calculated for histologically confirmed EAs within the SIM-defined BE group (SIR, 16.42; 95% CI, 8.20-29.38; $P < 0.001$). This is the first SIR calculated for the risk of EA from a SIM diagnosed BE population. The article by Solaymani-Dodaran et al. (3) does provide an estimate of 29.8 (95% CI, 10-106) but this was derived from a nonhistologically confirmed Barrett's population. The reasons for why this estimate was twice that of our analysis are not entirely obvious, particularly as a higher rate may be expected from a SIM diagnosed population, as opposed to a histologically unconfirmed one (1). It is possible that these point estimates for the U.K. and West Yorkshire reflect regional variations in the incidence of EA, as is known for this malignancy (32). Alternatively, the apparent inconsistency of these point estimates may be due to chance, as the span of the confidence interval for the Solaymani-Dodaran estimate is large and encompasses the point estimate derived from this cohort analysis.

The SIR analysis for colorectal cancer provided no evidence for an association with BE. This was despite the fact the analysis provided 100% and 82% power to detect the increases in risk previously proposed by Howden and Hornung (17) and Siersema et al. (33), respectively, given that the reported odds ratios were approximations to the relative risk. The Howden and Hornung (17) estimate was derived from a systematic review and meta-analysis of 685 patients with BE, whereas the study by Siersema et al. included 268 (33). This result, in addition to previous large studies with robust control groups (18, 19), is indicative of no association between BE and colorectal cancer.

The main limitation of this study is the use of the National Health Service Central Register as the sole data source. The completeness of this data set has previously been questioned, with estimates proposing that up to 5% of deaths and 10% of cancers may result in failed notification (34, 35). Despite these deficiencies, it is the only service that enables the provision of death and cancer events in a prospective manner and one may expect the proportion and pattern of missed registrations to be similar in both the flagged BE cohort and in the general population. Finally, routine data from the Northern and Yorkshire Cancer Registry and Information Service has been shown to have a much higher ascertainment level of incident cancers in comparison to the National data set as a whole or compared with many of the other regional registries (36, 37). Therefore, problems of incompleteness in the current study may be lower than previous citations indicate, consequently having a less significant effect on the proportion of failed notifications.

In summary, prospective follow-up of this BE cohort has substantiated the observations of an increased risk of esophageal cancer mortality it has also indicated that patients with BE may have an increased overall mortality rate not attributable to esophageal neoplasia. In addition, evidence has been presented that those who have a histologic BE diagnosis might also have an increased risk of circulatory disease mortality. The SIR analyses, meanwhile, have confirmed an elevated risk of esophageal cancer and esophageal adenocarcinoma in BE populations, while also providing evidence against any association with colorectal cancer.

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