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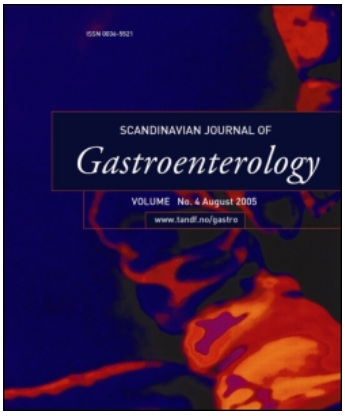

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ORIGINAL ARTICLE

Incidence of colorectal cancer in a population-based cohort of patients with Barrett's oesophagus

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Abstract

Objective. Previous studies have shown a positive association between colorectal cancer and Barrett's oesophagus, but this association is disputed. No population-based studies have examined the incidence of this cancer in patients with Barrett's oesophagus. ***Material and methods***. The present study comprised a population-based cohort of patients with Barrett's oesophagus (constructed using pathology reports of all oesophageal biopsies in Northern Ireland 1993–99; cohort subclassified according to whether specialized intestinal metaplasia (SIM) was present, absent, or not commented on in biopsies). Cases of colorectal cancer were identified by linking with the Northern Ireland Cancer Registry. The comparison group used was the general population in Northern Ireland. ***Results***. A total of 2969 patients with Barrett's oesophagus were followed for a total of 14,014 person-years (mean 4.7 years). SIM was present in 1670 patients (56.2%), absent in 545 (18.4%) and not commented on in 754 (25.4%). Colorectal cancer was diagnosed in 39 patients; 22 patients had cancer diagnosed at least 6 months after diagnosis of Barrett's oesophagus. There was no increased risk of colorectal cancer: the standardized incidence ratio (SIR) for cancer diagnosed at least 6 months after entry into the cohort was 0.82 (95% CI, 0.48–1.17); this risk did not alter with SIM status or gender. To assess a possible effect of diagnostic bias, we calculated SIRs for cancers occurring after at least 3 months, after at least 1 month and at any time after diagnosis of Barrett's oesophagus. These were 0.94 (0.57–1.30), 1.09 (0.69–1.48) and 1.46 (1.00–1.92), respectively. ***Conclusions***. The incidence of colorectal cancer was not elevated in patients with Barrett's oesophagus. Diagnostic bias may explain why previous studies have found an association.

Key Words: *Barrett's oesophagus, colorectal cancer, epidemiology, population-based study*

Introduction

Barrett's oesophagus (BO) is a condition in which the native squamous epithelium of the oesophagus is replaced by columnar epithelium, in response to chronic gastro-oesophageal reflux. It is the most important risk factor for oesophageal adenocarcinoma (OAC) [1]. In 1985, a report by Sontag et al. [2] suggested an association between colorectal neoplasia (adenomas and carcinoma) among patients with BO. Since then, there have been several studies supporting the association [3–5] and several refuting it [6–11]. Clarification of this issue is important for two reasons. First, if patients with BO have an increased risk of colorectal neoplasia, this has implications for eligibility for colorectal cancer screening. Secondly, if the association is true, searching for common aetiological factors may shed light on the causes of these conditions. Increased dietary fat intake and reduced fruit and vegetable intake are environmental factors implicated in CRC and possibly in BO [12], whilst p53 gene mutations occur in CRC and in the progression of BO to OAC [13].

There have been calls for a population-based study of colorectal cancer (CRC) incidence among patients with BO following a systematic review of published research in this area [5]. We undertook

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such a study to examine the incidence of CRC in a population-based cohort of patients with BO.

Material and methods

This study is a follow-up study of a population-based cohort of patients with BO. The cohort is comprised of every adult identified within Northern Ireland (NI), population 1.7.million, between 1993 and 1999 with columnar epithelium of the oesophagus. The cohort was constructed within the NI Cancer Registry by examining electronic pathology reports relating to every oesophageal biopsy undertaken within NI during this period. The reports contained information on the nature and site of the submitted biopsy specimens, the clinical summary recorded by the endoscopist on the request form, the full text of the pathologist's report on the specimen, and the pathologist's diagnosis. The clinical summaries of all oesophageal biopsies were examined and any that were taken at the oesophago-gastric junction (OGJ) were excluded. This step was taken to avoid including patients who inadvertently had mucosa from within a hiatal hernia biopsied. When it was not specifically stated that the biopsy was from the OGJ, it was assumed to have been taken from within the oesophagus.

Further classification of oesophageal biopsies

For the purposes of this study, BO was defined as the presence of columnar mucosa in the oesophagus, irrespective of whether columnar mucosa was stated as seen by the endoscopist. All oesophageal biopsies were further subdivided according to whether the pathologist stated that specialized intestinal metaplasia (SIM) was present or absent in the biopsy specimen. Any biopsy showing malignancy was excluded from the study.

Identification and classification of individual patients

A substantial number of patients in the cohort had oesophageal biopsies taken on more than one occasion. Individual patients were identified within the data set by matching on surname, forename(s) and date of birth (and hospital numbers when they were available). The date of the earliest biopsy showing columnar mucosa was taken as the date of entry into the cohort. Patients (rather than biopsies) were classified according to whether any of the oesophageal biopsies showed SIM. If at least one biopsy showed SIM, then the patient was classified as having BO with SIM. If the pathologist stated that SIM was not present in all available biopsies for a particular patient, then that patient was classified as having BO without SIM. For a substantial number of patients no specific comments were made regarding the presence or absence of SIM and these patients were classified as having BO with SIM status unknown.

Follow-up of patients

Deaths among the cohort were identified by matching with death files from the Registrar General's Office (NI) using the patient's surname, forename(s) and date of birth. These files contain information on all deaths that occur within NI. Cases of CRC occurring within the cohort before the end of December 2001 were identified by matching with the NI Cancer Registry database (using the patient's surname, forename(s), date of birth, and hospital numbers where available). This population-based cancer registry has collected data on all cancers occurring in NI residents since the beginning of 1993. Identification and verification of possible matches (where errors may have occurred when entering patient data on to a computer) were carried out by trained staff within the NI Cancer Registry.

Statistical methods

Person-years of follow-up were calculated for each member of the cohort with censoring either on the date of diagnosis of CRC, on the date of death, or on 31 December 2001. The incidence of CRC was calculated as the number of events divided by the person-years of follow-up. The standardized incidence ratio (SIR) for CRC was calculated by comparing the observed number of cancers in the cohort with the expected number calculated by applying 5-year age- and gender-specific CRC incidence rates in the NI population to the cohort. Confidence intervals (CIs) of rates and ratios were estimated from the Poisson distribution. In the principal analysis the SIR for CRC occurring at least 6 months after the diagnosis of BO was calculated. The SIRs for CRC diagnosed before 6 months were also calculated.

Results

The cohort comprised 2969 patients; 1670 (56.2%) with SIM, 545 (18.4%) without SIM and 754 (25.4%) whose SIM status was unknown; 1701 (57.3%) patients were men, and men were more likely than women to have had SIM (60.7% versus 50.3%, $\chi^2 = 31.7$, df 1, $p < 0.001$). Men were younger than women; mean age (Standard Deviation), 58.7 (14.9) years versus 64.6 (15.5) years, $t = 10.5$, $p < 0.001$ (independent samples t-test).

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The age and gender distribution of patients is shown in Figure 1.

Members of the cohort were followed-up for a mean of 4.7 years, for a total of 14,014 person-years of follow-up. Thirty-nine patients were diagnosed with CRC. Ten of these cancers were diagnosed at the same time or within the first month after diagnosis of BO, 4 at 1–3 months, 3 at 3–6 months, and 22 after 6 months. In the principal analyses, we excluded a diagnosis of CRC occurring within 6 months of a diagnosis of BO. This was to preclude any possible diagnostic bias arising from concurrent diagnosis of the two conditions. This resulted in a total of 13,005 person-years of follow-up. The incidence and SIR for CRC occurring at least 6 months after diagnosis of BO are presented in Table I. CRC incidence among patients with BO was not significantly different from that of the general population, and this did not differ by gender or by the presence of SIM. Using the method for power calculation for comparisons with an external standard, the study had 80% power to detect a SIR of 1.5 at 5% significance [14].

The SIRs (95% CI) for CRC occurring after at least 3 months, after at least 1 month and at any time after diagnosis of BO were 0.94 (0.57–1.30), 1.09 (0.69–1.48) and 1.46 (1.00–1.92), respectively (Figure 2).

Discussion

This is the first population-based study to assess the incidence of CRC in patients with BO. We found that the incidence of CRC was no higher in our cohort of 2969 patients with BO than that expected in the general population after an average follow-up of 4.7 years. Furthermore, this relationship did not differ according to gender or SIM status.

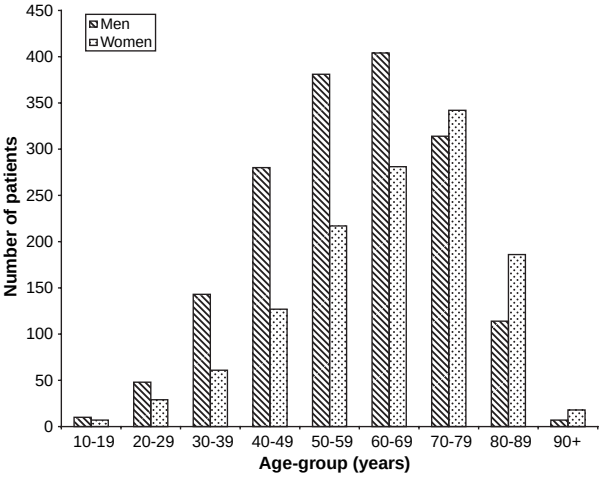

Figure 1. Age and gender distribution of patients within the Northern Ireland Barrett's cohort.

This study has a number of strengths. All patients studied had histologically confirmed columnar epithelium of the oesophagus, and every patient in whom this diagnosis was made in NI between 1993 and 1999 was included in the study. The population-based nature of this study precludes selection biases that may occur when only patients attending specific centres are investigated. Also, follow-up of patients is likely to be near-complete for two reasons: first, population-based cancer and death registers were used to determine deaths and cancer incidence among the cohort, and secondly, emigration from NI is uncommon, averaging 1.1% of the population per year in the period 1991–2003 [15]. Furthermore, there was no systematic colon screening carried out during the study period. Also, the NI Cancer Registry meets the stringent criteria necessary for inclusion in the IARC publication, "Cancer Incidence in Five Continents" [16]. The annual percentage of cases of CRC with microscopic verification was 86–89% during the study period, with low death certificate only case rates at 2–3%. Finally, the large size of the study allows the risk of CRC in BO to be estimated with greater accuracy than has previously been possible.

Even if there is no relationship between two conditions, an apparent association could arise simply because those two conditions are diagnosed at the same time. This diagnostic bias may be important when considering BO and CRC, since both conditions may be diagnosed concurrently during endoscopic examinations carried out to investigate various gastrointestinal symptoms and signs, such as anaemia. In our main analysis we therefore excluded CRC cases diagnosed within 6 months of the diagnosis of BO. The shorter the time between the diagnoses of BO and CRC, the more likely it is that diagnostic bias is operating. This explains the gradual increase in the SIR for CRC seen when cancers occurring after 3 months, after 1 month and at any time following the diagnosis of BO are included in the calculations. Diagnostic bias may also explain why some earlier studies have shown an increased risk of CRC in BO, since almost all previous studies included cases where these two diagnoses were made at the same time [2,3,6,8–10].

This study also has limitations. First, it is possible that some biopsies designated as oesophageal may have contained gastric mucosa taken from the OGJ or a hiatal hernia. If this were the case, some of the biopsies included in this study as showing BO could be normal gastric mucosa, which would lead to underestimation of the risk of CRC in BO. However, exclusion of biopsies labelled as taken from the OGJ should minimize this risk. Secondly, the length of follow-up was brief, and if the risk of CRC in BO

Table I. Incidence and standardized incidence ratio of CRC (6 months after diagnosis of Barrett's oesophagus) in the Northern Ireland Barrett's Register.

	No. of patients	Person-years of follow-up	No. of CRCs	Expected no. CRCs	Standardized incidence ratio for CRC (95% CI)
All patients	2,969	13,005	22	26.7	0.82 (0.48–1.17)
Men	1,701	7,377	12	16.6	0.72 (0.31–1.12)
Women	1,268	5,627	10	11.1	0.89 (0.34–1.45)
SIM present	1,670	7,574	14	16.7	0.84 (0.40–1.28)
SIM absent	545	2,125	2	3.47	0.58 (0–1.38)
SIM status unknown	745	3,306	6	6.47	0.93 (0.19–1.67)

Abbreviations: CRC = colorectal cancer; SIM = specialized intestinal metaplasia.

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increases substantially with time from diagnosis, we may have underestimated the risk of cancer. Nevertheless, if there is a true association between these two conditions, we would expect to find an increased risk of CRC in the current study. Thirdly, the possibility of "screening bias" must be considered. If a polyp or CRC was detected in patients undergoing gastrointestinal investigations for anaemia or non-specific symptoms, then it is possible that further investigation including oesophago-gastroduodenoscopy (OGD) might not be performed, or less attention might be paid to a segment of BO detected at OGD and biopsies not taken. If this occurred, then BO patients in the cohort would have a lower risk of CRC than all BO patients and a screening bias against detecting an increased risk of CRC in BO could have been introduced. Finally, 16 patients with a known previous diagnosis of CRC were included in the cohort, although others may have had an earlier diagnosis of CRC that was unknown to the NI Cancer Registry. If second CRC primaries in these patients were treated as recurrences then the risk of CRC may be underestimated in the cohort. However, as patients with colorectal cancer appear to have only a modestly increased risk of a second CRC primary (1.2-fold increased risk in women and a 2-fold increased risk in men) [17], which is highest among patients under 65 years of age, the magnitude of this potential bias is small.

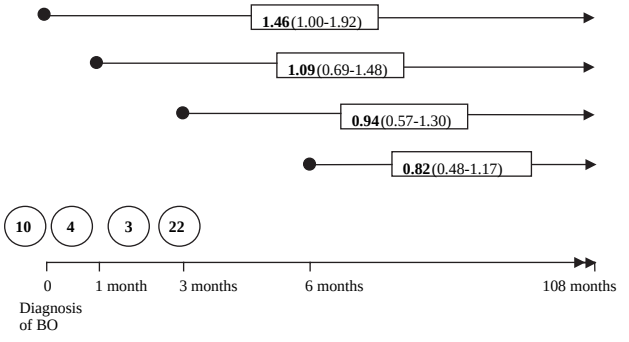

Figure 2. The effect of diagnostic bias. Numbers in circles represent number of cases of colorectal cancer diagnosed within the specified time period (e.g. 10 cases were diagnosed between 0 and 1 month following the diagnosis of BO (Barrett's oesophagus)). The standardized incidence ratio (SIR) (95% CI) can be seen to rise progressively as the follow-up period approaches the time of diagnosis of BO, indicating that diagnostic bias may be operating.

Previous studies looking at a possible association between BO and CRC have produced conflicting results. Earlier studies had no control group [2,6], which is likely to be an important factor. Howden & Hornung [5] carried out a systematic review of all published studies in 1995 but they were unable to perform a formal meta-analysis, even when considering only controlled studies. This was because of the variability in the control groups used in the studies, and the variability in the reported prevalence rates of CRC. As a result, they constructed a comparison cohort from four previously published studies of CRC screening in the general population. They found a significantly increased prevalence of CRC in BO, with a pooled odds ratio of 5.19 (CI 2.35–11.92).

Two studies have used cancer registry data to indirectly examine the relationship between BO and CRC. Vaughan et al. [4] used cancer registry data in the USA to look at the co-incidence of OAC and CRC. They found that patients with OAC had an increased risk of developing CRC, with an odds ratio of 1.44. Curiously though, this risk only applied to men, and there was a reduced risk in women. Lagergren & Nyren [11] did not find any increased risk of OAC among Swedish patients with CRC, and no important gender differences. However, OAC is a relatively rare cancer in Sweden, and this limited the power of the study to detect a weak association between the two conditions. Because we examined the risk of CRC in patients with BO, and not OAC, the power of our study was not influenced by the incidence of OAC.

If an association between BO and CRC exists, then increased mortality from CRC in patients with BO can be expected. However, we have previously

shown that mortality from CRC was not elevated in a cohort of BO patients [18], and a recent study has found similar findings [19].

In summary, we found no increase in the incidence of CRC in a cohort of patients with BO. Furthermore, our results suggest that diagnostic bias may explain why previous studies have found an association.

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