

## Ischemic heart disease, factor predisposing to Barrett's adenocarcinoma: A case control study

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### Abstract

**AIM:** To define the significance of ischemic heart disease (IHD) (stable angina to infarction) co-existence in Barrett esophagus (BE) patients and patients with esophageal adenocarcinoma (AdE).

**METHODS:** All BE/AdE patients in Blackpool-Wyre-Fylde area and Trikala prefecture identified from medical records. Patient clinical details were obtained from hospital and General Practitioner records. Additional information was gathered from validated questionnaire.

**RESULTS:** Forty (33%) AdE and 83 (19%) BE patients had IHD ( $P = 0.002$ ). Eighteen (15%) AdE and 34 (8%) BE patients had suffered a myocardial infarction ( $P = 0.03$ ). Three (3%) AdE and 7 (2%) BE patients had severe heart failure ( $P = 0.82$ ). Thirty-nine (47%) BE with IHD and 8 (20%) AdE patients with IHD consumed aspirin daily ( $P = 0.004$ ). Seventh-seven (93%) BE patients with IHD and 36 (90%) AdE patients with IHD were on statins ( $P = 0.86$ ). Logistic regression analysis: AdE was more frequent in the elderly, with long term

reflux, long BE and concurrent IHD (odds ratio: 2.086,  $P = 0.001$ ) not consuming statins. Eighteen (22%) BE patients with IHD [16 (84%) with myocardial infarction] vs 33 (10%) without IHD died from non-neoplastic causes within 24 mo from BE diagnosis ( $P = 0.005$ ).

**CONCLUSION:** IHD is more prevalent in AdE than BE patients. Increased prevalence of AdE is related with the presence of myocardial infarction but not severe heart failure, possibly because patients with BE and severe IHD have low life expectancy.

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**Key words:** Barrett esophagus; Esophageal adenocarcinoma; Ischemic heart disease; Myocardial infarction; Non-steroidal anti-inflammatory drugs

**Core tip:** Esophageal adenocarcinoma is a major health problem. We performed a population based retrospective comparison, shown that ischemic heart disease is twice as common among patients with esophageal adenocarcinoma than among those with uncomplicated Barrett esophagus. Although myocardial infarction was more frequently acquired in patients with esophageal adenocarcinoma, grade III or IV class heart failure was not, because patients with Barrett esophagus and severe heart failure usually have a low life expectancy and rarely survive longer than 2 years. Patients with Barrett esophagus and ischemic heart disease receive aspirin or nitrates every day more frequently than patients with esophageal adenocarcinoma.

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## INTRODUCTION

Gastro-esophageal reflux disease (GERD), a pathology characterized by reflux of gastric juice into the esophagus is rather common<sup>[1]</sup>. In case of prolonged and excessive GERD esophageal mucosa is replaced by metaplastic columnar epithelium. This condition is called Barrett's oesophagus (BE)<sup>[2]</sup>, and represents the main risk factor for esophageal adenocarcinoma (AdE) development<sup>[3]</sup>.

One of the main macroscopic features of BE is a net of new blood vessels formed within esophageal mucosa. Although Barrett's epithelium is mainly supplied from the submucosal lamina propria vasculature, presence of neovascularization emphasizes why BE is a precancerous lesion and why it can predispose to dysplasia and AdE development<sup>[4]</sup>. Barrett epithelium oxygen saturation remains high (approximately 90%) throughout the metaplastic process<sup>[5]</sup>, because microvasculature density rises stepwise as BE evolves towards AdE<sup>[6]</sup>. Esophageal inflammation enriches stromal angiogenesis<sup>[7]</sup>, while acid reflux causes periodic hypoxia<sup>[8]</sup>. Several markers of hypoxia, including oxygen-regulated transcription factor subunit hypoxia inducible factor-1 $\alpha$  and vascular endothelial growth factor, have been related to advanced BE<sup>[9,10]</sup>. Neovascularization markers, such as endoglin (CD-105), have been reported to be up-regulated in patients with high-grade dysplasia and AdE<sup>[11]</sup>.

It is not uncommon, to mix up esophageal with cardiac pain. Therefore GERD may be misclassified as ischemic heart disease (IHD) and vice versa<sup>[12]</sup>. Moreover GERD is rather common among patients with IHD, especially those with unstable angina<sup>[13]</sup>. Circulating angiogenic markers are increased in patients with IHD especially those with myocardial infarction (MI)<sup>[14]</sup> or severe congestive heart failure<sup>[15]</sup>. In addition, IHD could alter mucosal microcirculation causing topical ischemia<sup>[16]</sup> and through nitric oxide reduction, impairment of the mucosal defense<sup>[17]</sup> and mucosal adaptation to noxious stimuli<sup>[18]</sup>. Thus, it is expected that IHD might increase the risk of BE patients to develop AdE. Nevertheless, there are no data on the role of concurrent IHD in BE patients.

Our study aimed to calculate the prevalence of IHD (stable angina to infarction) in BE and AdE patients and study its significance in this patient group.

## MATERIALS AND METHODS

### BE-AdE case finding

The study included all BE or AdE cases, aged over 18 years living permanently either in Blackpool-Wyre-Fylde (BWF) NHS area (318886 inhabitants during 1991 census), between August 1, 1996 and July 31, 2001 or in the prefecture of Trikala (132689 inhabitants during 2001 census), between January 1, 2002 and December 31, 2005. Study design was similar in both study periods<sup>[19]</sup>. Endoscopy service was available only in Victoria Hospital in BWF, while it was available both in Trikala General Hospital and private services in Trikala prefecture. Nev-

ertheless we requested private service gastroenterologists to refer both BE and AdE cases in Trikala General Hospital during the study period. To secure complete case identification PT searched patient clinical notes, hospital endoscopy records, histology registers, operating theatre registers and death certificates to ascertain full case identification and gather a full clinical and drug history for every patient. General practitioners (GPs) and adjacent district hospitals were also contacted to provide additional cases who had an endoscopy outside the study hospitals during the study period as well as additional clinical information.

All BE or AdE subjects provided and completed an adapted and validated version of Reflux Symptom Questionnaire<sup>[20]</sup>, on their first visit after endoscopic and histological case verification. The study questionnaire provided clinical and drug details as described elsewhere<sup>[19]</sup>. For deceased patients the closest relative provided information to complete the study questionnaire. Thirty percent of patients failed to return the study questionnaire. We contacted them by phone and collected relevant data during the phone call.

For any discrepancy between questionnaire data and clinical records we favor the latter with the exception of over the counter non-steroidal anti-inflammatory drugs (NSAIDs) consumption, and deliberate ignorance to GP prescriptions.

### Patient characteristics

Patient characteristics definition has been described in detail elsewhere<sup>[19]</sup>. Thus, we recorded as active smokers all cases reporting any cigarette consumption the 10 year period preceding case recording. Total cigarette consumption recorded separately in pack-years. We recorded as alcohol abusers all cases consuming daily more than 50 g of pure alcohol the 10 year period preceding case recording. We recorded as NSAIDs consumers all cases consuming NSAIDs at least once a week the 10 year period preceding case recording. Daily NSAID consumption for at least 2 years NSAIDs users was recorded as daily one. Aspirin and non-aspirin NSAID consumption was recorded separately. Patients were considered users of nitrates, calcium channel blockers, beta blockers and statins if they consumed them at least 3 d/wk, the 10 year period preceding case recording. To avoid reverse causality, any medical therapy started less than 4 years before the study period was disregarded.

Based on body mass index (BMI) all cases were classified in 4 grades: grade 0: BMI < 20, grade 1: 20  $\leq$  BMI < 25, grade 2: 25  $\leq$  BMI < 30, grade 3: BMI  $\geq$  30.

We calculated the mean of frequency and duration of reflux recordings checked in every patient visit.

Diagnosis of ischemic heart disease (IHD) was based on clinical (angina), electrocardiographic, echocardiographic, scintigraphic and coronary arteriographic data. Hospitalizations for unstable angina or MI were recorded separately. PT and PI discussed objective findings and agreed IHD diagnosis. We used New York Heart Association Functional Classification to classify heart failure<sup>[21]</sup>.

We calculated socioeconomic status, as described by Ford *et al.*<sup>[22]</sup>, utilizing patient residential postcode and data from 1991 census (for BWF or 2001 Greek census for Greek patients). According to their socioeconomic status all cases were classified in three classes: lower, middle and high socioeconomic status.

### Endoscopy

We defined BE endoscopically as salmon pink mucosa extending at least 2 cm above the proximal end of the gastric folds. We measured BE length during endoscope withdrawal, and calculated tumor size measuring the distance between the two tumor edges and the incisors. Only adenocarcinomas co-existing with BE were included in case analysis and only when the centre of the tumour was over or above the gastroesophageal junction.

We recorded only hiatal hernias greater than 3 cm of length.

### Histology

During endoscopy we obtained biopsies in BE patients every 2 cm from all 4 quadrants. Presence of goblet cells and villi defined specialised epithelium<sup>[23]</sup>. We grades dysplasia as negative, low grade, high grade<sup>[24]</sup>. Cases with high grade dysplasia were not recorded as AdEs.

Two pathologists reviewed the pathology of all resected AdE specimens. Mucinous tumors, adenosquamous cancers, and poorly differentiated tumors not expressing cytokeratins 7 and 13 were excluded from the analysis.

### Ethics

Both BWF Ethics Committee and Trikala Hospital Scientific Council standing for Trikala Hospital Ethics Committee approved the study. All cases signed informed consent before entering the study.

### Statistical analysis

We used chi-square test with Yates' correction for non-parametric comparisons and student's *t*-test for parametric values. We overcame biases due to known risk factors using logistic regression analysis. Dependent parameters entered in the analysis were: age (per decade), male gender, BE length (per 5 cm), hiatal hernia length (per 5 cm), duration of reflux, daily use of aspirin, use of statins, high socioeconomic status. All of them represented well known risk factors for AdE development. We also evaluated the role of IHD. For each parameter we calculated the odds ratio (OR) and the corresponding 95%CI of OR.

Taking into consideration the results of a pilot study performed in BWF<sup>[25]</sup> and found that 20% of BE and 41% of AdE patients had IHD, we calculated that the study should include at least 36 BE patients with IHD to reach a power of 80%.

## RESULTS

### Patients

We found 193 patients with a lower esophageal adenocar-

cinoma in BWF. After histologic evaluation we excluded 30 (18%) patients with a tumor of the gastric cardia, 30 (18%) with an AdE without any co-existing BE, and 19 (12%) AdEs with scarce traces of BE. In the latter it was impossible to calculate Barrett length. We also found 10 lower esophageal adenocarcinomas in Trikala prefecture. We excluded 2 (20%) patients with a tumor of the gastric cardia and another 2 (20%) with an AdE without co-existing BE. Thus from the two hospitals 120 AdE patients were entered the study.

We identified 869 patients with salmon pink mucosa in the lower esophagus in BWF, compatible with BE. We excluded 238 (27%) patients because histologic definition was unavailable and 249 (39%) because histology reported the presence of fundic, cardiac or junctional mucosa instead of specialized columnar epithelium. We found another 78 patients with endoscopic BE in Trikala prefecture. We excluded 34 (44%) of them because histology identified only fundic, cardiac or junctional mucosa. Thus 426 BE patients were entered the study.

Both BE and AdE patients who entered the study were not different than those excluded (Table 1).

Patients with AdE were older than BE ones; presented a longer BE; which was less frequently co-existed with a hiatal hernia and they were complained for heartburn for a longer period of time (Table 2). Main demographic and BE related characteristics were independent to reflux complaints (Table 3).

### Patients with IHD

Forty (33%) AdE and 83 (19%) BE patients had IHD ( $P = 0.002$ ). Of them 18 (15%) AdE and 34 (8%) BE patients had suffered a MI ( $P = 0.03$ ), while 3 (3%) AdE and 7 (2%) BE patients had grade III or IV class heart failure ( $P = 0.82$ ).

Patients with IHD and AdE, when compared to BE patients with IHD were less frequently diabetics had consumed fewer cigarettes and had a longer reflux history. Forty-two (51%) BE patients with IHD and 12 (30%) AdE patients with IHD were on aspirin treatment ( $P = 0.03$ ). Of them 39 (47%) BE and 8 (20%) AdE patients consumed aspirin daily ( $P = 0.004$ ). Twelve (14%) BE patients with IHD and 20 (50%) AdE patients with IHD were on clopidogrel ( $P < 0.0001$ ). All of them persistent dyspepsia, when they have tried aspirin short-term. Twenty-nine (35%) BE patients with IHD had stopped antiplatelet treatment, due to persistent ulcerative lesions (14 duodenal ulcers, 8 gastric ulcers and 10 esophageal ulcers). Eight (20%) AdE patients with IHD had abandoned antiplatelet treatment ( $P = 0.14$ ); 3 due to persistent duodenal ulcer, 1 due to persistent gastric ulcer and 4 due to persistent esophageal ulcer. Seventy-seven (93%) BE patients with IHD were on statins for hyperlipidemia. Thirty-six (90%) AdE patients with IHD were also on statins ( $P = 0.86$ ). Six (7%) BE and 4 (10%) AdE patients had stopped statin treatment due to side effects ( $P = 0.86$ ), mainly elevation of transaminases, resolved after medication cessation. Seventy-nine (95%)

**Table 1 Clinical effects of aspirin in high risk population (clinical trials) *n* (%)**

Characteristics	Patients in the analysis	Patients excluded from the analysis	<i>P</i>
Patients with esophageal adenocarcinoma			
<i>n</i>	83	120	
Age [mean (SD)], yr	73 (SD = 11.3)	73 (SD = 11.5)	1.00
Male gender	73 (61)	58 (70)	0.19
Current smokers	44 (37)	33 (40)	0.66
Cig. Cons. (in PY) [mean (SD)]	22.5 (SD = 30.2)	22.1 (SD = 27.3)	0.92
Alcohol abusers	32 (27)	21 (25)	0.96
BMI ≥ 25	57 (48)	40 (47)	0.96
Presence of hiatus hernia	73 (61)	52 (63)	0.91
Ischemic heart disease	40 (33)	27 (33)	0.97
Use of aspirin	17 (14)	12 (14)	0.88
Low socioeconomic status	26 (22)	18 (22)	0.87
Dur of reflux [in Y-mean (SD)]	28.5 (SD = 10.1)	27.8 (SD = 12.2)	0.66
Freq of refl (d/wk) [mean (SD)]	5.4 (SD = 2.4)	5.4 (SD = 2.6)	1.00
Patients with Barrett's esophagus			
<i>n</i>	426	521	
Age [mean (SD)], yr	68 (SD = 14)	68 (SD = 13)	1.00
Male gender	264 (62)	316 (61)	0.73
Current smokers	136 (32)	174 (33)	0.68
Cig. Cons. (in PY) [mean (SD)]	19.8 (SD = 28.4)	20.3 (SD = 29.4)	0.79
Alcohol abusers	108 (25)	130 (25)	0.95
BMI ≥ 25	232 (54)	283 (54)	0.98
Barrett's length (in cm)	6.6 (SD = 3.9)	6.6 (SD = 3.7)	1.00
Presence of hiatus hernia	304 (71)	371 (71)	0.98
Ischemic heart disease	83 (19)	99 (19)	0.92
Use of aspirin	87 (20)	109 (21)	0.91
Low socioeconomic status	69 (16)	83 (16)	0.98
Dur of reflux [in Y-mean (SD)]	16.1 (SD = 9.9)	16.4 (SD = 10.2)	0.65
Freq of reflux (d/wk) [mean (SD)]	5.1 (SD = 2.3)	5.1 (SD = 2.5)	1.00

Cig. Cons.: Cigarette consumption in total throughout life; PY: Pack-years; BMI: Body mass index; Dur of reflux: Duration of reflux; Freq of refl (d/wk): Frequency of reflux episodes in days/week.

**Table 2 Comparison of the main demographic endoscopic and clinical characteristics between patients with Barrett's esophagus and esophageal adenocarcinoma *n* (%)**

Characteristics	Barrett's esophagus ( <i>n</i> = 426)	Esophageal adenocarcinoma ( <i>n</i> = 120)	<i>P</i>
Age [mean (SD)], yr	68 (SD = 14)	73 (SD = 11)	0.0003
Male gender	264 (61)	73 (61)	0.82
Smokers	136 (32)	44 (37)	0.39
Cig. Cons. (in PY) [mean (SD)]	19.8 (SD = 28.4)	22.5 (SD = 30.2)	0.36
Alcohol abusers	108 (25)	32 (27)	0.86
Barrett's length (in cm)	6.6 (SD = 3.9)	7.5 (SD = 4.2)	0.03
Presence of hiatus hernia	304 (71) <sup>1</sup>	73 (61)	0.04
BMI ≥ 25	232 (54)	57 (48)	0.21
Low socioeconomic status	69 (16)	26 (22)	0.21
Dur of reflux (in Y) [mean (SD)]	16.1 (SD = 9.9)	28.5 (SD = 10.1)	< 0.0001
Freq of reflux (d/wk) [mean (SD)]	5.1 (SD = 2.3)	5.4 (SD = 2.4)	0.21

<sup>1</sup>Thirty/fifty (60%) of patients with short segment Barrett present a hiatus hernia, as well as 5/10 (50%) with AdE on short segment Barrett esophagus. Y: Years; Cig. Cons.: Cigarette consumption in total throughout life; PY: Pack-years; BMI: Body mass index; Dur of reflux: Duration of reflux; Freq of reflux (d/wk): Frequency of reflux episodes in days/week.

BE patients with IHD and 37 (93%) AdE patients with IHD were on beta-blockers ( $P = 0.85$ ). Sixty-two (75%) BE patients with IHD and 19 (47%) AdE patients with IHD were on sphincter relaxing medication ( $P = 0.005$ ). Of them 57 (69%) BE and 14 (35%) AdE patients were on nitrates ( $P = 0.0004$ ), while 15 (18%) BE and 15 (38%) AdE patients were on calcium channel blockers ( $P = 0.02$ ). Main risk factors and treatment receiving in BE

and AdE patients with IHD are presenting in Table 4.

### Logistic regression analysis

Logistic regression analysis in the whole study population revealed that AdE was more frequent in the elderly; in those with long term reflux complaints; with longer BE and and in those with concurrent IHD (odds ratio: 2.086, 95%CI: 1.339-2.257,  $P = 0.001$ ), AdE was less frequent



**Table 3** Comparison of the main demographic endoscopic and clinical characteristics between patients with Barrett esophagus without reflux symptoms and those with gastroesophageal reflux *n* (%)

Characteristics	Asymptomatic patients <i>n</i> = 40	Patients with GERD <i>n</i> = 386	<i>P</i>
Age [mean (SD)], yr	68 (SD = 8)	68 (SD = 15)	0.50
Male gender	28 (70)	236 (61)	0.35
Smokers	17 (43)	119 (31)	0.18
Cig. Cons. (in PY) [mean (SD)]	22.7 (SD = 29.6)	17.4 (SD = 25.6)	0.12
Alcohol abusers	13 (33)	95 (25)	0.37
Barrett's length (in cm)	7.4 (SD = 5.1)	6.6 (SD = 3.9)	0.12
Presence of hiatus hernia	26 (65)	278 (72)	0.45
BMI $\geq$ 25	18 (45)	214 (55)	0.27
Low socioeconomic status	7 (18)	62 (16)	0.99

GERD: Gastroesophageal reflux disease; Cig. Cons.: Cigarette consumption in total throughout life; PY: Pack-years; BMI: Body mass index.

**Table 4** Main demographic and disease related characteristics and treatment received in patients with ischemic heart disease and Barrett esophagus or esophageal adenocarcinoma *n* (%)

Characteristic	BE <i>n</i> = 83	AdE <i>n</i> = 40	<i>P</i>
Age [mean (SD)], yr	75 (SD = 10)	78 (SD = 10)	0.12
Male gender	54 (65)	23 (58)	0.54
Active smokers	23 (28)	10 (25)	0.92
Alcohol abusers	18 (22)	8 (20)	0.98
Cig. Cons. (in PY) [mean (SD)]	43 (SD = 25)	33 (SD = 17)	0.02
Low socioeconomic status	21 (25)	12 (30)	0.74
Diabetes	16 (19)	1 (3)	0.02
Barrett's length (in cm)	6.4 (SD = 3.6)	7.1 (SD = 4.4)	0.35
Presence of hiatal hernia	55 (66)	27 (68)	0.95
Hyperlipidemia under treatment	77 (93)	36 (90)	0.86
Hypertension	58 (70)	30 (75)	0.71
Dur ref (in years) [mean (SD)]	19 (SD = 10)	28 (SD = 10)	< 0.0001
Freq ref (d/wk): [mean (SD)]	5.3 (SD = 2.3)	6 (SD = 2)	0.1
BMI $\geq$ 25	45 (54)	19 (48)	0.61
Use of beta-blockers	79 (95)	37 (93)	0.85
Sphincter relaxing medication	62 (75)	19 (47)	0.005
Low dose aspirin	42 (51)	12 (30)	0.03
Low dose aspirin daily	39 (47)	8 (20)	0.004

Cig. Cons.: Cigarette consumption in total throughout life; PY: Pack years; BMI: Body mass index; Dur ref: Duration of reflux; Freq ref (d/wk): Frequency of reflux episodes; BE: Barrett esophagus; AdE: Esophageal adenocarcinoma.

in statin consumers (Table 5).

### Follow-up

Nineteenth (23%) BE patients with IHD *vs* 33 (10%) without IHD died from non-neoplastic causes within 24 mo from BE diagnosis (*P* = 0.002). Sixteen (84%) BE patients with IHD who deceased within 2 years from BE diagnosis, had suffered a MI or had grade III or IV class heart failure (*P* = 0.01).

## DISCUSSION

We performed a population based retrospective study and found that IHD was almost twice as frequent in AdE patients as those with uncomplicated BE. Although MI was more frequently acquired in AdE patients, grade III

or IV class heart failure was not, because the majority of BE patients with severe heart failure do not survive longer than 2 years. BE patients with IHD consumed aspirin daily and nitrates more frequently than AdE patients and calcium channel blocker less frequently.

Despite its population-based design and thorough case evaluation our study has several drawbacks. It is retrospective, and not large enough to draw strong conclusions.

Patients with AdE have no choice but to come to medical attention. On the other hand BE patients are usually referred for endoscopy only if they present severe persistent GERD. It is very difficult to exclude reference related biases, nevertheless a small minority of BE patients without GERD were referred for endoscopy<sup>[26]</sup> and we can speculate the features of BE population escaping medical attention by studying this population. We have shown that patients with BE and reflux symptoms were not different than BE patients without reflux in various demographic and disease related characteristics. Thus, we expect that our study population might be representative of the total BE population in BWF.

It is still uncertain whether the presence of specialized epithelium in the lower esophagus is exclusively related to AdE development<sup>[27]</sup>. Some authorities believe intestinal metaplasia absence is only a reflection of sampling error and that it will invariably be present if meticulously searched<sup>[28]</sup>. Nevertheless, the risk of non-columnar intestinal metaplasia to progress to AdE is still debatable<sup>[29]</sup>. By excluding patients without a histological verification of intestinal metaplasia, we limited our BE population and increasing bias due to BE underreporting. On the other hand, because there was no difference between patients included and those excluded from the analysis in any demographic or disease related characteristic, we avoided bias related to poor defined cases or overestimation of BE length due to esophageal inflammation.

Over-expression of various angiogenetic factors, such as hypoxia-inducible factor or vascular endothelial growth factor permits human myocardium to adapt to coronary ischemia<sup>[30]</sup>. Nevertheless, as those angiogenetic factors enter general circulation they can produce BE

**Table 5** Logistic regression analysis, in the whole study population, for known risk factors for esophageal adenocarcinoma development, various conditions co-existing with non-steroidal anti-inflammatory drugs use and various subgroups of non-steroidal anti-inflammatory drugs use

Variable	Odds ratio	CI of odds ratio	P
Age (per decade)	1.315	1.220-1.514	<0.001
Male gender	0.946	0.622-1.437	0.75
BE length (per 5 cm)	1.289	1.043-1.547	0.045
Length of HH (per 5 cm)	0.924	0.847-1.007	0.06
Duration of reflux (in decades)	1.848	1.686-2.060	<0.001
IHD	2.086	1.339-3.257	0.001
Daily aspirin use	0.623	0.346-1.111	0.65
Use of statins	0.576	0.356-0.918	0.02
Low socioeconomic status	1.411	0.844-2.351	0.43

IHD: Ischaemic heart disease; BE: Barrett esophagus.

hyperproliferation and augment BE malignant potential<sup>[4]</sup>. After all, tissue hypoxia has been related to cancer development<sup>[31]</sup> and epidermal growth factor up-regulation due to cardiac ischemia<sup>[32]</sup>, can favor carcinogenesis within BE<sup>[33]</sup>. Finally, oxidative phosphorylation up-regulation<sup>[34]</sup> and subsequent reactive oxygen species overproduction, due to peripheral hypoperfusion increases the mutagenic pressure and raises genetic instability<sup>[35]</sup>. Thus, we expected and we found that IHD is more frequently acquired in AdE than BE patients, especially those suffered an MI.

Old age is more prevalent in AdE patients and IHD is a disease of old age<sup>[36]</sup>. Thus it is possible that higher IHD incidence in AdE patients is solely a result of old age. Nevertheless, IHD was an independent risk factor for AdE in multiple regression analysis and pathogenetic mechanisms support a deleterious effect of IHD in BE patients.

Deleterious effect of IHD on BE progression to malignancy is balanced by reduced life expectancy of those patients, especially those with severe heart failure<sup>[37]</sup>. In concordance to Moayyedi *et al.*<sup>[38]</sup> we have reported a high mortality in BE patients with concurrent IHD, especially those with a MI or with severe heart failure.

Observational study data from BE patients are disappointing concerning aspirin protective effect. Both our case control study in BE/AdE patients<sup>[19]</sup> and Kastelein *et al.*<sup>[39]</sup> prospective study identified no protection from low-dose aspirin use in BE patients. Opposing our findings in general BE population, daily aspirin use in BE patients with IHD seems to be beneficial, possibly because of it improves cardiac and peripheral circulation and prevents over-expression of angiogenetic factors.

Epidemiological data agree that statin use could protect BE patients from AdE development<sup>[39-42]</sup>. Although use of statins was less frequent in AdE than BE patients, its use was almost universal in patients with IHD, preventing identification of their possible beneficial properties.

We have already reported, in concordance with Ladanchuk *et al.*<sup>[43]</sup> that nitrates have no influence in BE patients<sup>[19]</sup>. Nevertheless, we found that nitrates had a beneficial role in BE patients with IHD. Beneficial role of nitrates/sphincter relaxing medication in BE patients with

IHD could be incidental, mirroring not a truly protective relationship but the small number of patients studied. Nevertheless it could also be a result of cardiac and peripheral perfusion improvement after nitrate use.

In conclusion IHD is more prevalent in AdE than BE patients. Use of low-dose aspirin and nitrates in this study group is encouraging. More studies are needed to show if IHD is more frequent in BE patients because they are older or verify that IHD is deleterious for BE patients and unveil the pathogenetic mechanisms (increase of angiogenetic and growth factors) beneath it. Those studies should be prospective, multicentric and large enough to overcome possible biases faced in our study.

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## COMMENTS

### Background

Gastro-esophageal reflux disease is a common condition resulting from reflux of gastric or intestinal contents into the esophagus. Prolonged reflux may lead to replacement of esophageal lining by pathological lining resembling large bowel, a condition known as Barrett's oesophagus. The most serious complication of Barrett's oesophagus is the development of esophageal adenocarcinoma. Barrett's lining is characterised by the presence of pathological vessels and overproduction of various substances promoting the production of pathological vessels. Such substances are overproduced in ischemic heart disease. No studies today have addressed any correlation of Barrett's esophagus to ischemic heart disease. People only know that ischemic heart disease is the main cause of death in Barrett's patients.

### Research frontiers

Various substances promoting the production of pathological vessels have a key role in the development of esophageal adenocarcinoma in patients with Barrett's esophagus. Population studies suggest that aspirin and statins, to cornerstones of ischemic heart disease treatment can prevent the development of esophageal adenocarcinoma in patients with Barrett's esophagus.

### Innovations and breakthroughs

This study has shown that ischemic heart disease was almost twice as frequent in cancer patients as those with uncomplicated Barrett's esophagus. Myocardial infarction, as severe complication of ischemic heart disease was more frequent as well. Severe heart failure was not, because the majority of Barrett's esophagus patients do not survive longer than 2 years. Barrett patients more frequently used daily aspirin and nitrate use with ischemic heart disease than patients with esophageal adenocarcinoma.

### Applications

Patients with Barrett's esophagus and ischemic heart disease deserve more frequent endoscopies in order to identify esophageal adenocarcinoma early. Aspirin and statin treatment is useful in this patient group and can reduce the risk to develop esophageal adenocarcinoma.

### Peer review

This is an excellent study as it's the first report to explore the relationship be-

tween ischemic heart disease and Barrett esophageal adenocarcinoma. The case control study was well designed and carried out, and the manuscript is clearly written. The results are believable, and the conclusions are acceptable.

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