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RAPID COMMUNICATION

Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: Results from the FINBAR study

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Abstract

AIM: To investigate risk factors associated with Barrett's oesophagus and oesophageal adenocarcinoma.

METHODS: This all-Ireland population-based case-control study recruited 224 Barrett's oesophagus patients, 227 oesophageal adenocarcinoma patients and 260 controls. All participants underwent a structured interview with information obtained about potential lifestyle and environmental risk factors.

RESULTS: Gastro-oesophageal reflux was associated with Barrett's [OR 12.0 (95% CI 7.64-18.7)] and oesophageal adenocarcinoma [OR 3.48 (95% CI 2.25-5.41)]. Oesophageal adenocarcinoma patients were more likely than controls to be ex- or current smokers [OR 1.72 (95% CI 1.06-2.81) and OR 4.84 (95% CI 2.72-8.61) respectively] and to have a high body mass index [OR 2.69 (95% CI 1.62-4.46)]. No significant associations were observed between these risk factors and Barrett's oesophagus. Fruit but not vegetables were negatively associated with oesophageal adenocarcinoma [OR 0.50 (95% CI 0.30-0.86)].

CONCLUSION: A high body mass index, a diet low in fruit and cigarette smoking may be involved in the progression from Barrett's oesophagus to oesophageal adenocarcinoma.

Key words: Barrett's oesophagus; Oesophageal adenocarcinoma; Smoking; Gastro-oesophageal reflux; Body mass index; Diet; Case-control

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INTRODUCTION

Barrett's oesophagus, a condition of the distal oesophagus in which the normal stratified squamous epithelium is replaced by specialised intestinal metaplasia, is a recognized precursor of oesophageal adenocarcinoma[1], a cancer that has been increasing in incidence in many Western societies over recent decades[2-6]. It is unknown if all oesophageal adenocarcinomas arise from Barrett's oesophagus but there is some evidence to suggest that this is the case[7]. In surveillance programs of Barrett's oesophagus only a minority of patients develop oesophageal adenocarcinoma[8-12] raising the question of what factors are implicated in the development of oesophageal adenocarcinoma from Barrett's oesophagus.

Several case-control studies have investigated lifestyle factors associated with oesophageal adenocarcinoma[13-19] but few studies of factors associated with Barrett's oesophagus have been reported[20-22]. Gastro-oesophageal reflux is strongly associated with oesophageal adenocarcinoma[14-17,23,24] and is thought to be the main predisposing factor for Barrett's oesophagus[20]. A small proportion of gastro-oesophageal reflux sufferers develop Barrett's oesophagus[25-28] and approximately 0.5% of Barrett's oesophagus patients progress to oesophageal adenocarcinoma each year[8,29-31] indicating that factors apart from gastro-oesophageal reflux are involved in the development of Barrett's oesophagus and in its progression to oesophageal adenocarcinoma. Several risk factors for oesophageal adenocarcinoma have been established, including a high body mass index (BMI)[15,16,24,32-34], smoking[13,15,19,34,35] and possibly a diet low in fruit and vegetables[16,24,36-38]. Engel *et al*[39] estimated that these three factors, in combination with gastro-oesophageal reflux, have a population attributable risk for

oesophageal adenocarcinoma of 78.7%. However, it is not clear at which stage along the oesophageal inflammation-metaplasia-adenocarcinoma sequence these factors exert their effect. Studies comparing risk factors for Barrett's oesophagus and oesophageal adenocarcinoma provide the opportunity to examine whether these risk factors are important in the development of Barrett's oesophagus or in its progression to oesophageal adenocarcinoma. This is crucial to the targeting of preventive efforts aimed at reducing the morbidity and mortality associated with these conditions. We undertook a population-based case-control study of Barrett's oesophagus and oesophageal adenocarcinoma within Ireland.

MATERIALS AND METHODS

Study details have been described in detail elsewhere[40]. Briefly, the Factors Influencing the Barrett's Adenocarcinoma Relationship (FINBAR) study recruited three groups of subjects: (1) patients with oesophageal adenocarcinoma, (2) patients with long-segment Barrett's oesophagus, and (3) normal population controls between March 2002 and December 2004.

Oesophageal adenocarcinoma cases had histological confirmation of adenocarcinoma within the oesophagus. Northern Ireland cases were identified from electronic pathology records from all pathology laboratories within the province. Republic of Ireland cases were identified from the main hospitals involved in the diagnosis and treatment of oesophageal cancer. All available relevant clinical and histological records including endoscopy, surgical and radiological reports were reviewed by LAA, SJM, JM and a pathologist, to confirm that the tumour was located in the oesophagus and to assign tumours into two groups: (1) oesophageal tumours (including tumours encroaching on the esophagogastric junction) and (2) junctional tumours (tumours involving the oesophagus, esophagogastric junction and gastric cardia).

Barrett's oesophagus patients were eligible for inclusion if $\geqslant$ 3 centimetres of typical Barrett's mucosa were seen at endoscopy and the presence of specialised intestinal metaplasia was confirmed by histological examination of biopsy specimens. Incident and prevalent cases were included and subjects were frequency matched to the age and 5-year sex distribution of oesophageal adenocarcinoma patients. Patients with dysplasia on histological examination were excluded. In Northern Ireland, cases of Barrett's oesophagus were initially identified from pathology reports gathered from throughout Northern Ireland. Endoscopy note review was necessary in most patients to confirm the length of the segment of Barrett's oesophagus, as length was infrequently recorded on the pathology report. In the Republic of Ireland, clinicians in the Dublin and Cork areas sent details of Barrett's oesophagus patients who met the inclusion criteria to the research personnel.

Eligible control subjects were adults without a history of oesophageal or other gastro-intestinal cancer or a known diagnosis of Barrett's oesophagus and were frequency matched, by sex and 5-year age band, to the distribution of oesophageal adenocarcinoma patients. Northern Ireland controls were selected at random from the General Practice Master Index (a province-wide database of all persons registered with a general practitioner) and Republic of Ireland controls were selected at random from four General Practices (two urban and two rural) in the Dublin and Cork areas chosen by the researchers to reflect the urban/rural distribution of oesophageal adenocarcinoma patients in the Republic of Ireland.

Participants underwent a structured interview with trained interviewers after giving informed written consent. Information obtained included data on symptoms of gastro-oesophageal reflux (questions based on a translation of those used by Lagergren *et al*[14] in their Swedish case-control study), weight 5 years before the interview, height and weight at age 21, maximum and minimum weight during adulthood, smoking history, education, occupation and alcohol consumption. Anthropometric measures (height, weight, waist and hip circumference) were taken at the time of interview.

Frequent gastro-oesophageal reflux was defined as symptoms of heartburn and/or acid reflux occurring more than 50 times per year (at least once per week), more than 5 years prior to the interview. Frequent gastro-oesophageal reflux, which prevented subjects from going to sleep or awoke them from sleep, was classified as nocturnal gastro-oesophageal reflux symptoms. The reflux symptom score used by Lagergren *et al*[14] was applied to the FINBAR dataset but scores 1-4 were combined in the analyses because of the small number of subjects in the first 2 categories.

Current BMI and BMI 5 years before the interview date were calculated by dividing weight in kilograms (current measured and 5-year self-reported, respectively) by current height in metres squared. BMI at age 21 was calculated by dividing self-reported weight in kilograms at age 21 by self-reported height in meters at age 21 squared.

Current smoking status was defined as having smoked at least one cigarette per day for 6 mo or longer, 5 years before the interview date. Previous smokers were those who had quit smoking more than 5 years prior to the interview date. People who had never smoked, and those who had smoked less than 100 cigarettes in their lifetime, or less than one cigarette per day for 6 mo or longer were defined as never smokers. Pack years of smoking were calculated by multiplying the number of cigarettes smoked per day by the number of years of smoking, and dividing by 20. Cigar and pipe smokers were those who had ever smoked at least one cigar or one pipe-full of tobacco per week irrespective of whether they smoked cigarettes.

Fruit, vegetable and energy intake were measured using the European Prospective Investigation of Cancer (EPIC) food frequency questionnaire used in the Norfolk area of England[41] as part of a large European cancer cohort study. This validated questionnaire was modified for the Irish population by including foods commonly eaten in Ireland as identified in the recent North/South Food Consumption Survey[42]. Fruit and vegetable consumption 5 years prior to the interview date were quantified in terms of the sum of the frequencies that each item of fruit/vegetable was eaten per week.

Table 1 Characteristics of controls, Barrett's and oesophageal adenocarcinoma patients

Variables	Controls	Barrett's oesophagus	*P* (BO *vs* controls)	Oesophageal adenocarcinoma	*P* (OAC *vs* controls)
Sex , *n* (%)			0.548		0.992
Male	220 (84.6)	185 (82.6)		192 (84.6)	
Female	40 (15.4)	39 (17.4)		35 (15.4)	
Age			0.567		0.276
Mean years	63	62.4		64.2	
Education			0.013		< 0.001
Years (full-time)	12	11.3		10.7	
Job type			0.016		0.013
Manual	119 (48.0)	130 (59.1)		128 (59.5)	
Non-manual	129 (52.0)	90 (40.9)		87 (40.5)	
Alcohol, *n* (%)			0.135		0.004
Never	69 (26.5)	57 (25.6)		65 (28.9)	
Ever	191 (73.5)	166 (74.4)		160 (71.1)	
Mean (grams/d)	26.1	22.3		19.2	
GOR frequent, *n* (%)			< 0.01		< 0.001
Never	211 (81.2)	60 (26.8)		117 (51.5)	
Ever	49 (18.8)	164 (73.2)		110 (48.5)	
Body mass index			0.895		< 0.001
Mean	27	27		28.7	
Fruit			< 0.001		< 0.001
Frequency per week	14.2	11.9		11.2	
Vegetables			0.04		0.348
Frequency per week	20	18.7		20.6	
Total energy intake (kcal)			0.036		0.023
Mean	2573.9	2727.2		2744.2	
Smoking status, *n* (%)			0.4		< 0.001
Never	102 (40.2)	87 (39.2)		45 (20.4)	
Ex-smoker	107 (42.1)	85 (38.3)		99 (44.8)	
Current	45 (17.7)	50 (22.5)		77 (34.8)	

BO: Barrett's oesophagus; OAC: oesophageal adenocarcinoma; GOR: gastro-oesophageal reflux.

Statistical analysis

Throughout the article exposures of interest are presented in tertiles. Tertiles of BMI, for example, were calculated from the normal control group with all subjects categorised according to these tertiles. Statistical analyses were performed using STATA 8.0[43]. Chi-square tests were used to examine differences between groups for categorical variables and t-tests were used for continuous variables. Unconditional maximum-likelihood multinomial (polytomous) logistic regression analyses were undertaken to examine the associations between the exposure variables of interest and case/control status adjusting for potential confounders; odds ratios (OR) with 95% confidence intervals (CI) were calculated. Analyses are shown adjusted for potential confounders, including sex, age at interview, job type (manual, non-manual work), education (years full-time) and alcohol consumption (grams per week). Further adjustment was made for gastro-oesophageal reflux symptoms (never, ever), smoking (current, ex-, never), BMI (5 years before diagnosis/interview) and total energy intake (in kilocalories) where appropriate.

Ethical approval for the FINBAR study was obtained from the Research Ethics Committee of the Queen's University Belfast, the Clinical Research Ethics Committee of the Cork Teaching Hospitals and the Research Ethics Committee Board of St. James's Hospital, Dublin.

RESULTS

Two hundred and twenty-four Barrett's oesophagus patients, 227 oesophageal adenocarcinoma patients and 260 controls were recruited. One hundred and thirty-one (57.7%) of the oesophageal adenocarcinoma patients were classified as having oesophageal tumours, ninety-two (40.5%) were classified as junctional tumours and insufficient evidence was available to classify the position of 4 (1.8%) tumours. Characteristics of patients and controls are shown in Table 1.

The participation rate of eligible, alive oesophageal adenocarcinoma patients was 74.2% and the overall response rate was 63.9%. The participation rates among Barrett's oesophagus patients and controls were 82.4% and 41.8%, respectively.

Gastro-oesophageal reflux

Symptoms of gastro-oesophageal reflux more than 5 years prior to the interview date were strongly associated with Barrett's oesophagus and to a lesser extent with oesophageal adenocarcinoma (Table 2). In total 72.8% of Barrett's patients, 48.5% of oesophageal adenocarcinoma patients and 18.9% of controls reported at least weekly symptoms of gastro-oesophageal reflux. Barrett's oesophagus and oesophageal adenocarcinoma patients were more likely than controls to report nocturnal gastro-oesophageal reflux symptoms, although in the oesophageal adenocarcinoma group the association did not hold for those with junctional tumours (chi-square test, $P = 0.001$).

Using the symptom scoring system developed by Lagergren *et al*[14] Barrett's patients were 18 times, and oesophageal adenocarcinoma patients more than 3 times,

Table 2 Comparison of gastro-oesophageal reflux symptoms between controls and Barrett's oesophagus and oesophageal adenocarcinoma patients and between oesophageal and junctional tumour subgroups

	Controls No.	BE No.	Adjusted1 OR (95% CI)	EAC No.	Adjusted[1] OR (95% CI)	Oesophageal tumours No.	Adjusted[1] OR (95% CI)	Junctional tumours No.	Adjusted[1] OR (95% CI)
Frequent GOR[2]									
No	211	60	1.00	117	1.00	64	1.00	51	1.00
Yes	49	164	12.0 (7.64 to 18.7)	110	3.48 (2.25 to 5.41)	67	3.73 (2.27 to 6.13)	41	3.12 (1.79 to 5.43)
Nocturnal symptoms[3]									
No	237	110	1.00	167	1.00	86	1.00	79	1.00
Yes	23	113	10.9 (6.49 to 18.5)	60	3.16 (1.81 to 5.51)	45	4.53 (2.49 to 8.22)	13	1.45 (0.67 to 3.14)
Reflux symptom score[4]									
No GOR	211	54	1.00	116	1.00	63	1.00	51	1.00
1-4 points	25	63	10.4 (5.90 to 18.5)	53	3.63 (2.06 to 6.40)	22	2.59 (1.30 to 5.15)	30	4.99 (2.58 to 9.62)
4.5-6.5 points	24	107	18.4 (10.5 to 32.3)	58	3.55 (2.02 to 6.27)	46	5.11 (2.78 to 9.38)	11	1.52 (0.66 to 3.47)
Symptom frequency in tertiles (*t*/yr)									
No GOR	211	61	1.00	117	1.00	64	1.00	51	1.00
< 208	17	44	9.34 (4.88 to 17.9)	33	2.94 (1.50 to 5.77)	18	2.96 (1.38 to 6.35)	14	2.81 (1.23 to 6.41)
208-365	23	50	7.86 (4.36 to 14.2)	35	2.75 (1.49 to 5.07)	18	2.53 (1.23 to 5.19)	16	2.94 (1.38 to 6.29)
> 365	9	69	29.2 (13.3 to 64.5)	42	6.54 (2.93 to 14.6)	31	8.20 (3.51 to 19.1)	11	4.50 (1.69 to 12.0)
Duration of symptoms in tertiles (yr)									
No GOR	211	54	1.00	116	1.00	63	1.00	51	1.00
< 10	18	64	11.9 (6.37 to 22.1)	39	3.67 (1.94 to 6.97)	16	2.67 (1.25 to 5.72)	22	5.00 (2.38 to 10.5)
10-22.6	15	38	8.09 (4.09 to 16.0)	21	2.28 (1.08 to 4.83)	18	3.57 (1.62 to 7.86)	3	0.78 (0.21 to 2.88)
> 22.6	16	68	16.0 (8.38 to 30.5)	51	4.41 (2.30 to 8.48)	34	5.11 (2.51 to 10.4)	16	3.41 (1.52 to 7.65)

BO: Barrett's oesophagus; OAC: oesophageal adenocarcinoma; GOR: gastro-oesophageal reflux; OR: odds ratio; CI: confidence interval. [1]Adjusted for sex, age at interview date, body mass index (5 yr prior to the interview date), smoking status (never, ex-, current), alcohol intake (grams), years of full-time education and job type (manual, non-manual). [2]Symptoms of heartburn and/or reflux more than 50 times per year. [3]Symptoms of GOR that prevented sleep or woke the person from sleep. [4]Reflux symptom score[14]. Heartburn or regurgitation only = 1 point, GOR symptoms 2 to 6 times per week = 1 point, heartburn and regurgitation = 1.5 points, nightly symptoms = 2 points, GOR symptoms 7 to 15 times per week = 2 points, symptoms more than 15 times per week = 3 points.

as likely as controls to have a score in the highest gastro-oesophageal reflux category. Patients defined as having oesophageal tumours experienced more severe gastro-oesophageal reflux than patients defined as having junctional tumours. Barrett's oesophagus and oesophageal adenocarcinoma patients were more likely to have suffered from gastro-oesophageal reflux on a more frequent basis and for a longer duration of time than controls (Table 2).

Body mass index

The associations between BMI (in tertiles) and risk of Barrett's oesophagus and oesophageal adenocarcinoma at the time of interview are displayed in Table 3. No associations were observed between Barrett's oesophagus and BMI at any stage (current, at 5 years prior to the interview date or at age 21). Current BMI was significantly lower in oesophageal adenocarcinoma patients than in controls, most likely due to cancer-associated weight loss. However, high BMI 5 years prior to the interview date was associated with a more than 2-fold increased risk of oesophageal adenocarcinoma. The association was similar (highest tertile vs lowest) for tumours classified as oesophageal [OR 2.54 (95% CI 1.44 to 4.48)] or junctional [OR 2.95 (95% CI 1.52 to 5.72]. Oesophageal adenocarcinoma patients were also more likely than controls to be in the highest tertile of BMI at age 21 and to have a higher maximum and minimum weight than controls. Adjusting any of the BMI analyses for a history of gastro-oesophageal reflux symptoms did not significantly alter the observed associations (Table 3).

Similar results were observed when BMI was categorised according to the World Health Organisation classification system[44]. Barrett's oesophagus patients were no more likely than controls to be currently overweight (25-30 kg/m^2) [OR 0.86 (95% CI 0.55 to 1.36)] or obese (> 30 kg/m^2) [OR 1.06 (95% CI 0.62 to 1.81)] or to have been overweight or obese 5 years before the interview date [OR 0.95 (95% CI 0.62 to 1.45)] and [OR 0.80 (95% CI 0.47 to 1.38) respectively]. Oesophageal adenocarcinoma patients were currently less overweight/obese than controls [OR 0.36 (95% CI 0.23 to 0.57) and OR 0.39 (95% CI 0.22 to 0.69), respectively], but were more likely to have been overweight or obese 5 years before the interview date [OR 1.55 (95% CI 0.96 to 2.50) and OR 2.55 (95% CI 1.47 to 4.41) respectively].

Waist-hip ratio was measured at the time of interview, and no relationship was observed between waist-hip ratio and oesophageal adenocarcinoma [(highest tertile vs lowest) OR 0.80 (95% CI 0.50 to 1.28)] or Barrett's oesophagus [OR 1.09 (95% CI 0.68 to 1.73)].

Fruit and vegetable intake

Barrett's oesophagus patients appeared to be less likely than controls to consume fruit and/or vegetables (Table 4). However, following adjustment for gastro-oesophageal reflux symptoms neither fruit nor vegetable intake alone was significantly associated with Barrett's oesophagus. Compared to controls oesophageal adenocarcinoma patients had a lower intake of fruit, but not vegetables (Table 4). There was no significant difference in the consumption of fruit and vegetables between the oesophageal and junctional subgroups (chi-squared test, $P = 0.691$).

Table 3 Body mass index and weight comparisons between controls and Barrett's oesophagus and oesophageal adenocarcinoma patients

	Controls	Barrett's oesophagus			Oesophageal adenocarcinoma		
	No.	No.	Adjusted[1] OR (95% CI)	Further adjusted for GOR OR (95% CI)	No.	Adjusted[1] OR (95% CI)	Further adjusted for GOR OR (95% CI)
Current BMI in tertiles (kg/m^2)							
< 25.8	86	77	1.00	1.00	115	1.00	1.00
25.8-29.0	87	64	0.75 (0.47 to 1.19)	0.61 (0.36 to 1.03)	54	0.38 (0.24 to 0.62)	0.35 (0.21 to 0.58)
> 29.0	85	82	0.97 (0.61 to 1.52)	0.75 (0.44 to 1.25)	50	0.38 (0.23 to 0.62)	0.33 (0.20 to 0.56)
BMI 5 yr ago in tertiles (kg/m^2)							
< 25.0	86	75	1.00	1.00	51	1.00	1.00
25.0-28.1	87	78	1.02 (0.65 to 1.61)	0.84 (0.50 to 1.42)	55	1.23 (0.72 to 2.08)	1.74 (0.66 to 1.97)
> 28.1	86	71	0.89 (0.56 to 1.41)	0.85 (0.51 to 1.44)	120	2.70 (1.65 to 4.41)	2.69 (1.62 to 4.46)
BMI age 21 in tertiles (kg/m^2)							
< 22.1	81	70	1.00	1.00	55	1.00	1.00
22.1-24.1	88	80	0.96 (0.61 to 1.52)	1.17 (0.70 to 1.99)	64	0.97 (0.59 to 1.60)	1.10 (0.65 to 1.85)
> 24.1	84	69	0.83 (0.51 to 1.33)	1.04 (0.61 to 1.79)	96	1.59 (0.97 to 2.59)	1.81 (1.08 to 3.02)
Maximum weight in tertiles (kg)[2]							
< 73	87	72	1.00	1.00	53	1.00	1.00
73-86	91	89	1.21 (0.76 to 1.95)	1.04 (0.61 to 1.79)	67	1.54 (0.90 to 2.61)	1.42 (0.83 to 2.45)
> 86	80	62	0.98 (0.58 to 1.66)	0.91 (0.50 to 1.66)	104	3.44 (1.97 to 5.98)	3.32 (1.88 to 5.86)
Minimum weight in tertiles (kg)[2]							
< 64	108	102	1.00	1.00	79	1.00	1.00
64-70	81	61	0.83 (0.52 to 1.34)	1.00 (0.58 to 1.72)	52	1.10 (0.65 to 1.86)	1.20 (0.70 to 2.08)
> 70	70	60	0.97 (0.57 to 1.64)	1.25 (0.69 to 2.27)	95	2.83 (1.63 to 4.89)	3.22 (1.82 to 5.71)

GOR: gastro-oesophageal reflux; OR: odds ratio; CI: confidence interval. [1]Adjusted for sex, age at interview date, smoking status (never, ex-, current), alcohol intake (grams), years of full-time education and job type (manual, non-manual). [2]Also adjusted for height (centimetres). [b]$P \leq 0.001$.

Table 4 Comparison of fruit and vegetable consumption (5 yr before interview date) between controls and Barrett's oesophagus and oesophageal adenocarcinoma patients

	Controls	Barrett's Oesophagus			Oesophageal adenocarcinoma		
	No.	No.	Adjusted[1] OR (95% CI)	Adjusted[1] + GOR OR (95% CI)	No.	Adjusted[1] OR (95% CI)	Adjusted[1] + GOR OR (95% CI)
Fruit and vegetables (portions/wk)							
<20	85	105	1.00	1.00	98	1.00	1.00
20-34	86	58	0.58 (0.36 to 0.92)	0.50 (0.30 to 0.84)	61	0.64 (0.39 to 1.04)	0.60 (0.36 to 1.00)
> 34	86	60	0.61 (0.38 to 0.98)	0.67 (0.40 to 1.15)	65	0.67 (0.41 to 1.12)	0.71 (0.43 to 1.19)
Fruit (portions/wk)							
< 5	83	94	1.00	1.00	109	1.00	1.00
5-20	87	76	0.78 (0.49 to 1.23)	0.91 (0.55 to 1.51)	63	0.52 (0.32 to 0.85)	0.56 (0.34 to 0.92)
> 20	87	53	0.57 (0.35 to 0.94)	0.64 (0.37 to 1.12)	53	0.47 (0.28 to 0.80)	0.50 (0.30 to 0.86)
Vegetables (portions/wk)							
< 12	83	90	1.00	1.00	66	1.00	1.00
12-17	85	68	0.76 (0.48 to 1.21)	0.75 (0.45 to 1.25)	71	1.13 (0.68 to 1.86)	1.12 (0.67 to 1.87)
> 17	89	65	0.72 (0.44 to 1.15)	0.82 (0.48 to 1.39)	87	1.38 (0.84 to 2.28)	1.49 (0.89 to 2.48)

GOR: gastro-oesophageal reflux; OR: odds ratio; CI: confidence interval. [1]Adjusted for sex, age at interview date, smoking status (never, ex-, current), alcohol intake (grams), energy intake (kilocalories), body mass index (5 yr prior to interview), years of full-time education and job type (manual, non-manual).

Smoking

Cigarette Smoking was not significantly associated with Barrett's oesophagus; however there was a strong relationship between smoking and oesophageal adenocarcinoma (Table 5). The findings remained significant regardless of the method of smoking categorisation. Adjusting for symptoms of gastro-oesophageal reflux did not significantly alter the observed associations. Ex-smoking and current smoking status 5 years prior to interview were similar in both the oesophageal [OR 1.86 (95% CI 1.05 to 3.30) and OR 4.62 (95% CI 2.40 to 8.91) respectively] and junctional subgroups [OR 1.80 (95% CI 0.95 to 3.42) and OR 4.68 (95% CI 2.40 to 8.91) respectively, chi-square test, $P = 0.951$]. Neither pipe smoking nor cigar smoking was significantly associated with oesophageal adenocarcinoma or Barrett's oesophagus (Table 5).

DISCUSSION

This is the first reported population-based case-control study to compare risk factors for both Barrett's oesophagus and oesophageal adenocarcinoma. The study confirms established risk factors for oesophageal adenocarcinoma and demonstrates important differences between Barrett's oesophagus and oesophageal adenocarcinoma in their

Table 5 Smoking in controls, Barrett's oesophagus and oesophageal adenocarcinoma patients

	Controls	Barrett's oesophagus			Oesophageal adenocarcinoma		
	No.	No.	Adjusted[1] OR (95% CI)	Further adjusted for GOR OR (95% CI)	No.	Adjusted[1] OR (95% CI)	Further adjusted for GOR OR (95% CI)
Smoking status (5 yr prior to interview)							
Never[2]	102	87	1.00	1.00	46	1.00	1.00
Ex-smoker	107	85	0.97 (0.63 to 1.49)	0.86 (0.53 to 1.40)	99	1.85 (1.15 to 2.97)	1.72 (1.06 to 2.81)
Current smoker	45	50	1.27 (0.74 to 2.17)	1.41 (0.77 to 2.58)	77	4.64 (2.64 to 8.17)	4.84 (2.72 to 8.61)
No. of cigarettes smoked per day							
Never[2]	102	87	1.00	1.00	46	1.00	1.00
< 15	54	41	0.94 (0.57-1.57)	0.98 (0.55 to 1.75)	44	1.85 (1.07-3.20)	1.87 (1.06 to 3.28)
15-20	51	41	0.98 (0.58-1.65)	0.94 (0.52 to 1.69)	67	3.14 (1.83-5.37)	3.05 (1.76 to 5.30)
> 20	49	53	1.32 (0.78-2.22)	1.16 (0.65 to 2.09)	66	2.92 (1.68-5.10)	2.72 (1.54 to 4.80)
Duration of smoking (yr)							
Never[2]	102	87	1.00	1.00	46	1.00	1.00
< 20	47	28	0.72 (0.41 to 1.28)	0.72 (0.38 to 1.38)	38	1.92 (1.07 to 3.44)	1.91 (1.05 to 3.48)
20-35	55	57	1.21 (0.74 to 1.98)	1.09 (0.62 to 1.90)	54	2.08 (1.21 to 3.58)	1.94 (1.11 to 3.38)
> 35	53	51	1.18 (0.70 to 1.98)	1.18 (0.66 to 2.11)	85	3.74 (2.18 to 6.40)	3.71 (2.14 to 6.42)
Years since quitting smoking							
Never[2]	102	87	1.00	1.00	46	1.00	1.00
< 26	27	29	1.27 (0.74 to 2.19)	1.42 (0.78 to 2.60)	36	4.72 (2.68 to 8.31)	4.89 (2.74 to 8.71)
26-41	40	32	1.26 (0.68 to 2.33)	1.11 (0.56 to 2.20)	29	2.68 (1.42 to 5.07)	2.51 (1.30 to 4.83)
> 41	40	24	1.02 (0.58 to 1.81)	0.89 (0.47 to 1.70)	34	1.52 (0.82 to 2.85)	1.40 (0.74 to 2.66)
Pack years of smoking							
Never[2]	102	87	1.00	1.00	46	1.00	1.00
< 15	48	36	0.92 (0.54 to 1.57)	0.94 (0.51 to 1.72)	30	1.39 (0.76 to 2.55)	1.39 (0.75 to 2.58)
15-40	55	47	1.01 (0.61 to 1.67)	0.92 (0.52 to 1.63)	68	2.95 (1.74 to 5.00)	2.84 (1.66 to 4.86)
> 40	51	52	1.28 (0.76 to 2.17)	1.23 (0.68 to 2.21)	79	3.48 (2.01 to 6.02)	3.34 (1.91 to 5.83)
Cigar							
Never	234	204	1.00	1.00	194	1.00	1.00
Ever	22	18	0.84 (0.41 to 1.71)[3]	0.73 (0.33 to 1.61)[3]	29	1.30 (0.67 to 2.53)[3]	1.22 (0.61 to 2.43)[3]
Pipe							
Never	233	194	1.00	1.00	182	1.00	1.00
Ever	23	28	1.68 (0.88 to 3.20)[3]	1.31 (0.64 to 2.68)[3]	41	1.64 (0.88 to 3.06)[3]	1.45 (0.77 to 2.75)[3]

GOR: gastro-oesophageal reflux; OR: odds ratio; CI: confidence interval. [1]Adjusted for sex, age at interview date, body mass index 5 yr prior to the interview date, alcohol intake (grams), years of full-time education and job type (manual, non-manual). [2]Never smoked, smoked less than 100 cigarettes in lifetime or smoked less than 1 cigarette per day for 6 mo in their lifetime [3]Adjusted for use of other tobacco products e.g. cigarettes, pipe or cigar respectively.

association with these factors. Gastro-oesophageal reflux symptoms were strongly associated with Barrett's oesophagus and to a lesser extent with oesophageal adenocarcinoma. A high BMI, 5 years prior to the interview date, and smoking were significantly associated with an increased risk of oesophageal adenocarcinoma but not Barrett's oesophagus. Barrett's oesophagus patients appeared to eat less fruit and vegetables than controls. A diet high in fruit but not in vegetables was associated with a reduced risk of oesophageal adenocarcinoma. These data may suggest that gastro-oesophageal reflux symptoms and possibly a diet low in fruit and vegetables are initially responsible for the development of Barrett' s oesophagus, and that obesity and smoking are involved in the progression of Barrett's oesophagus to oesophageal adenocarcinoma.

The strengths of the FINBAR study are its population-based design, the rapid case ascertainment and stringent inclusion criteria for Barrett's oesophagus (specialised intestinal metaplasia, length $\geqslant$ 3 centimetres) which minimise the inclusion of subjects with a biopsy from an unrecognized hiatus hernia.

In this study, cancers were divided into two subgroups: oesophageal tumours (which could encroach on, but not involve, the oesophagogastric junction) and tumours involving the oesophagus, oesophagogastric junction and gastric cardia (termed junctional tumours). There was a potential weakness for some misclassification of oesophageal adenocarcinoma patients in this study as it was impossible to determine whether junctional tumours are truly gastric or oesophageal in origin.

A potential weakness of the study was the low response rate amongst controls, which may have introduced selection bias. However, controls were similar to the general population with regards to symptoms of gastro-oesophageal reflux and BMI. In a study from Bristol, 15.6% of people aged 20-59 had weekly symptoms of heartburn[45] compared to 18.4% of controls within this age range in the FINBAR study. If gastro-oesophageal reflux symptoms were over-represented in controls then the actual associations between gastro-oesophageal reflux, Barrett's oesophagus and oesophageal adenocarcinoma may be stronger than observed in this study. The mean weight and the proportion of the obese controls were similar to those seen in the all-Ireland Food Consumption Survey (1997 to 1999)[46]. Mean BMI in males aged 51-64 years in the survey was 27.6 kg/m^2 (s.d. 3.6 kg/m^2) and in FINBAR 28.0 kg/m^2 (s.d. 4.5 kg/m^2). Similarly, 20% of men were obese (BMI > 30.0 kg/m^2) in the Food Consumption Survey compared to 22% of FINBAR male

controls. However, in the 2001 Northern Ireland health and social wellbeing survey[47] 23.6% of males at the age of 55 years or over were current smokers, 53.1% ex-smokers and 23.3% non-smokers compared to 18.9%, 48% and 31.1% respectively in FINBAR controls. Non-smokers may be overrepresented among FINBAR controls which could lead to an overestimation of the positive association between oesophageal adenocarcinoma and smoking.

The main predisposing risk factor for Barrett's oesophagus is gastro-oesophageal reflux. Our finding of a strong association between gastro-oesophageal reflux symptoms and Barrett's oesophagus is in agreement with a previous case-control study by Conio *et al*[20]. Since the main presenting symptom for Barrett's oesophagus is gastro-oesophageal reflux it is possible that diagnosed Barrett's oesophagus patients are not representative of all Barrett's patients with regards to gastro-oesophageal reflux symptoms. The association is likely causal in nature; however there may be an overestimation of the true association between gastro-oesophageal reflux and Barrett's oesophagus. Although the exact mechanisms by which gastro-oesophageal reflux causes Barrett's oesophagus are still not fully understood, reflux of acid and/or bile into the distal oesophagus is believed to damage the native squamous epithelium and result in re-epithelisation with columnar mucosa. The strength of the relationship between gastro-oesophageal reflux symptoms and oesophageal adenocarcinoma, is in keeping with the findings of several studies on Barrett's oesophagus[17,23,48] except that of Lagergren *et al*[14] who reported an OR of 7.7. Our data suggest that although gastro-oesophageal reflux is common in patients with tumours classified as either oesophageal or junctional, those with junctional tumours seem to have less severe symptoms. In particular, nocturnal symptoms of gastro-oesophageal reflux are more strongly associated with oesophageal but not with junctional tumours.

Obesity has been linked with the development of gastro-oesophageal reflux[45,49,50], increased intra-abdominal pressures[54,55] and relaxation of the lower oesophageal sphincter[56] which may worsen gastro-oesophageal reflux symptoms. Obesity has been increasing in incidence[51-53], paralleling the increasing incidence of oesophageal adenocarcinoma[2-6].

Some studies have suggested that a high BMI is associated with an increased risk of Barrett's oesophagus[22,57,58], although Caygill *et al*[58] suggested that obesity is only a risk factor for Barrett's oesophagus in young people. No associations were observed between current BMI, BMI 5 years prior to the interview date, or BMI at age 21, and Barrett's oesophagus in the FINBAR study. It is possible that the BMI of controls was higher than that of the population which could explain the fact that no association was observed. However, a high BMI 5 years prior to the interview date was associated with a 2.5 fold increased risk of oesophageal adenocarcinoma, which is similar to reports in other case-control studies[24,32-34,59]. If BMI is not associated with Barrett's oesophagus then one possible mechanism for the association between BMI and oesophageal adenocarcinoma may be through the increased production of free insulin-like growth factor-1 in obese subjects, which stimulates cell proliferation and inhibits apoptosis[60,61]. Sohda *et al*[62] suggested that increased free insulin-like growth factor-1 may be associated with the development of oesophageal cancer. In Barrett's patients increased expression of insulin-like growth factor-1 receptor is associated with neoplastic progression[63].

Fruit, although not vegetable intake was significantly associated with a reduced risk of oesophageal adenocarcinoma in this study. A diet high in fruit and vegetables has been shown to be able to protect against a number of cancers[64], including cancers of the digestive tract[65]. Several case-control studies have specifically reported positive associations between high fruit and/or vegetable intake and a reduced risk of oesophageal adeno carcinoma[16,24,36-38] and a cohort study recently reported a non-significant inverse association between oesophageal adenocarcinoma and vegetables and citrus fruit[66]. In the FINBAR study vegetable consumption was not associated with a reduced risk of oesophageal adenocarcinoma in fact the OR was raised [OR 1.49 (95% CI 0.89 to 2.48)]. One possible explanation for the apparent protective effect of fruit against oesophageal adenocarcinoma may be that patients with gastro-oesophageal reflux avoid certain fruits which can aggravate their symptoms. However, the protective association between fruit (and overall fruit/vegetable) consumption and oesophageal adenocarcinoma remains after adjustment for gastro-oesophageal reflux symptoms. Fruit and vegetables are high in anti-oxidants, especially in vitamin C, dietary intake of which is reduced in oesophageal adenocarcinoma patients[38,67-70]. Tissue levels of vitamin C are also lower in areas of specialised intestinal metaplasia than in squamous mucosa suggesting that oxidative stress may be implicated in the neoplastic progression of Barrett's oesophagus[71]. Reflux of gastric contents into the oesophagus can enhance the production of free radicals which may cause damage to lipids, proteins and DNA through oxidative stress and may be implicated in the development of Barrett's oesophagus and/or oesophageal adenocarcinoma.

Smoking has been associated with an increase in gastro-oesophageal reflux symptoms in some studies[50,72,73], but not in others[20,58,74,75]. Unlike Smith *et al*[57] we observed no significant association between smoking and Barrett's oesophagus in the FINBAR study. There was a strong relationship between smoking and oesophageal adenocarcinoma with a slightly higher OR than observed in previous studies[13,15,16,18,19,35,76]. The under-representation of current smokers among FINBAR controls may tend to overestimate the association between smoking and oesophageal adenocarcinoma/Barrett's oesophagus but should not affect the difference in ORs seen between the two conditions. Our data suggest that smoking may influence the progression of Barrett's oesophagus to oesophageal adenocarcinoma and not the initiation of Barrett's oesophagus. One possible explanation may be that the higher rate of cell division and proliferation of columnar epithelial cells[77] and the malignant potential that such cells possess[78], may be promoted by carcinogenic (or DNA damaging) compounds from cigarette smoke. Olliver *et al*[79] showed that Barrett's mucosa has higher levels of DNA damage

than squamous epithelium and smoking is associated with increased DNA damage in Barrett's mucosa[80].

In conclusion, our data indicate that gastro-oesophageal reflux is a risk factor for oesophageal adenocarcinoma and demonstrate the high proportion of diagnosed Barrett's patients with gastro-oesophageal reflux symptoms. In the FINBAR study oesophageal adenocarcinoma differs from Barrett's oesophagus by being associated with high BMI and smoking. These factors could be implicated in the development of oesophageal adenocarcinoma from Barrett's oesophagus although further observational and interventional studies are required to confirm or refute our findings. It is hoped that these findings will help direct future research into the mechanisms underlying oesophageal adenocarcinoma and the development of prevention strategies.

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