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Adenocarcinoma of the oesophagus and gastric cardia: Male preponderance in association with obesity

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ABSTRACT

Recent evidence links obesity with the rising incidence of oesophageal adenocarcinoma. In Ireland between 1995 and 2004 the incidence of oesophageal adenocarcinoma increased by 38%, and this coincided with a 67% increase in the prevalence of obesity. In this study, a prospective case-control study was undertaken in 760 patients presenting to a tertiary centre between 1994 and 2004 diagnosed with cancer of the oesophagus, gastric cardia or stomach. Data were compared with 893 healthy controls. Multivariate logistic regression models were used to calculate the odds ratio (OR) of developing either cancer type according to quartiles of body mass index (BMI). Based on pre-illness BMI, 82% of patients who developed adenocarcinoma of the oesophagus were either overweight or obese compared with 59% of the healthy control population ($P < 0.001$). A dose-dependent relationship existed between BMI and oesophageal adenocarcinoma in males. The adjusted odds ratio was 4.3 (95% CI: 2.3–7.9) among males in the highest BMI quartile compared with males in the lowest quartile ($P < 0.001$ for trend). Using common cut-off points for BMI, the OR of adenocarcinoma of the lower oesophagus was 11.3 times higher (95% CI: 3.5–36.4) for individuals with a BMI >30 kg/m^2 versus individuals with a BMI <22 kg/m^2 ($P < 0.001$ for trend). For adenocarcinoma of the gastric cardia, males in the top quartile of BMI had an OR of 3.5 (95% CI: 1.3–9.4) compared with the lowest quartile ($P = 0.03$ for trend). A significant ($P < 0.001$) inverse relationship between BMI and oesophageal SCC was observed.

The odds ratio for adenocarcinoma of the oesophagus, the oesophago-gastric junction and gastric cardia rose significantly with increasing BMI. For tumours of the lower oesophagus, obesity increased the risk 10.9-fold. The increased risk is significant in males only.

1. Introduction

The patterns of oesophageal cancer in Europe and North America are changing rapidly. The incidence of oesophageal adenocarcinoma is increasing by 5–10% per year.[1] The striking increased trends seen in adenocarcinoma of the oesophagus and gastric cardia are thought to result from several modifiable and interrelated risk factors, including chronic gastro-oesophageal reflux disease, poor diet, *H. pylori* eradication, and obesity.[1–3] A recent study of population attributable risks for oesophageal adenocarcinoma linked being overweight to 41% of cases.[3]

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The Republic of Ireland has witnessed a marked increase in the prevalence of obesity since the early 1990s, and 67% of men and 75% of women over the age of 51 are now overweight or obese.[4] During this same period there was a 38% increase in the number of cases of oesophageal adenocarcinoma registered by the National Cancer Registry of Ireland.[5] The incidence rate of oesophageal cancer in Ireland is amongst the highest in the western world with 11.7 cases per 100 000 males and 6.1 cases per 100 000 females compared with a European Union average of 9.5/100 000 for males and 2.2/100 000 for females.[5] The aim of this study was to examine the impact of Body Mass Index (BMI) and obesity on the risk of upper gastrointestinal cancer in Irish subjects.

2. Patients and methods

All histologically confirmed cases of adenocarcinoma and squamous cell carcinoma (SCC) of the oesophagus, oesophago-gastric junction, gastric cardia, and stomach, diagnosed or treated at the Oesophageal Unit of St. James's Hospital, Dublin between 1994 and 2004 were included. This Unit treats approximately 35% of patients in the Republic of Ireland with tumours at these sites, and approximately 50% of referrals can be treated with curative intent.

The tumour location was based on endoscopic and radiological assessment. Tumours at the oesophago-gastric junction were designated after pathological resection as Types I–III, as per Siewert and colleagues[6] Type I was adenocarcinoma of the distal oesophagus involving the junction, usually arising in specialised intestinal metaplasia; Type II tumours are centred at the oesophago-gastric junction; and Type III is a gastric carcinoma infiltrating the oesophago-gastric junction and distal oesophagus from below. In this study, Types I and II represent the O–G junction tumours, and Type III denotes a gastric cardia tumour.

A registered Dietitian assessed every patient individually, and a detailed history and anthropometric measurements were documented including height, weight at diagnosis, BMI at diagnosis, pre-illness weight, and pre-illness BMI. For cancer cases, the patient's pre-illness BMI was calculated from usual body weight at least one year prior to diagnosis. The medical, dietetic and histopathology records of the cancer cases were recorded on a computerised upper Gastrointestinal Cancer Database (Patient Analysis and Tracking System™, Dendrite Clinical Systems, UK). Data recorded concerned age, sex, tumour site, pathology, smoking and alcohol intakes, co-morbid disease, socio-economic status, reflux symptoms, medications, and the presence or absence of Barrett's oesophagus. *H. pylori* status was available in a small percentage of cases. Adiposity was estimated by BMI, computed as weight in kilograms divided by height in meters squared (kg/m^2). BMI was defined using the World Health Organisation definitions,[7] with a BMI of 20–24.9 kg/m^2 normal, overweight 25–29.9 kg/m^2, and obese >30 kg/m^2.

Anthropometric data on 893 healthy controls were used for comparison – controls under the age of 65 years were obtained from nationwide data as part of the North/South Ireland Food Consumption Survey,[4] and over 65 year-old controls were interviewed and nutritionally assessed by a registered dietitian at several day centres for the elderly in Dublin. Weight, height and BMI were calculated, and data regarding cigarette and alcohol consumption, and socio-economic status gathered. Information on reflux history and *H. pylori* status was not available in the control group, and therefore could not be considered in this study.

2.1. Statistical analysis

Pre-illness BMI was grouped into quartiles for analysis based on BMI distributions amongst the controls subjects. Relative risks according to anthropometric status were expressed as odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression models. We tested for linear trend by including BMI as a continuous risk factor in the logistic regression. We investigated the linearity of any possible association between BMI and risk of cancer using a flexible model fitting approach that used a restricted cubic spline model with knots at the 25th, 50th, and 75th percentiles of BMI in the controls. All analyses were adjusted for the effects of age sex, cigarette consumption (current smoker, ex-smoker, never smoker), and heavy alcohol (>14 units/week women, >21 units week men). Data was analysed in STATA™ (version 8.2, Stata-Corp LP). The logistic regression analysis was also repeated excluding patients with Barrett's Oesophagus and gastro-oesophageal reflux disease.

3. Results

The sample population consisted of 239 females and 521 males, 508 patients had adenocarcinoma and 252 had SCC of the oesophagus. Tumour sites were lower oesophagus (n = 279), mid oesophagus (n = 91), oesophago-gastric junction (n = 142), upper oesophagus (n = 26), gastric cardia (n = 65), and fundus, body or distal stomach (n = 157).

3.1. Nutritional status pre-illness

Based on pre-illness BMI, 82% of adenocarcinoma patients were overweight or obese versus 35% of patients with SCC ($P < 0.001$). The median pre-illness BMI of males who developed ACA of the oesophagus was 28 kg/m^2 (IQ 25.5–31.8 kg/m^2) versus 24 kg/m^2 (IQ 21.3–26.6 kg/m^2) for SCC ($P < 0.001$). Males who developed ACA of the oesophagus were significantly heavier than healthy controls that had a median BMI of 25.8 kg/m^2 (IQ 23.8–28.7 kg/m^2), $P < 0.001$. SCC cases had a pre-illness BMI that was significantly lighter than healthy controls and ACA cases ($P < 0.001$) (see Fig. 1).

3.2. Adenocarcinoma of the oesophagus and oesophago-gastric junction

The median pre-illness BMI for patients who developed adenocarcinoma of the oesophagus was 28 kg/m^2 (IQ 25.5–31.8 kg/m^2). This was significantly greater than healthy controls (median BMI 25.8 kg/m^2, IQ 23.8–28.7 kg/m^2, $P < 0.001$). Patients with tumours in the lower oesophagus and the oesophago-gastric junction were the heaviest (28.1 kg/m^2, IQ 25.9–32.1 kg/m^2; 27.8 kg/m^2, IQ 25.1–31.1 kg/m^2, respectively). Subjects were divided into four categories using the 25th, 50th, and 75th centiles of BMI among healthy controls. (<23.8 kg/m^2 quartile

Table 1 – Odds ratios (OR) and 95% confidence intervals (CI s) associated with pre-illness body mass index (BMI) by sex[a] for adenocarcinoma

Factor	Oesophageal adenocarcinoma		Lower oesophageal adenocarcinoma		OG junction adenocarcinoma	
	Case/controls	OR (95% CI)	No	OR (95% CI)	No	OR (95% CI)
Males and females						
Pre-illness BMI						
Quartile 1	40/223	1.0 (referent)	13/223	1.0 (referent)	24/223	1.0 (referent)
Quartile 2	43/222	1.0 (0.6–1.7)	24/222	2.2 (0.9–5.3)	19/222	0.7 (0.3–1.4)
Quartile 3	74/225	1.9 (1.1–3.3)	44/225	5.0 (2.1–11.4)	28/225	1.3 (0.7–2.5)
Quartile 4	131/223	3.0 (1.8–5.0)	74/223	7.2 (3.2–16.2)	54/223	2.2 (1.2–4.0)
Test for trend		$P < 0.001$	$P < 0.001$		$P = 0.001$	
Males only						
Pre-illness BMI						
Quartile 1	27/74	1.0 (referent)	9/74	1.0 (referent)	17/74	1.0 (referent)
Quartile 2	38/96	1.4 (0.7–2.8)	22/96	3.2 (1.3–8.9)	16/96	0.8 (0.4–1.9)
Quartile 3	60/115	2.3 (1.3–4.6)	35/115	5.9 (2.1–16.1)	25/115	1.7 (0.8–3.7)
Quartile 4	114/110	4.3 (2.3–7.9)	62/110	9.1 (3.4–24.3)	49/110	2.9 (1.4–6.1)
Test for trend		$P = 0.0001$	$P = 0.0001$		$P = 0.001$	
Females only						
Pre-illness BMI						
Quartile 1	13/149	1.0 (referent)	4/149	1.0 (referent)	7/149	1.0 (referent)
Quartile 2	5/126	0.4 (0.1–1.3)	2/126	0.6 (0.1–4)	3/126	0.5 (0.1–1.9)
Quartile 3	14/110	1.4 (0.5–3.5)	9/110	3.2 (0.8–13.8)	3/110	0.5 (0.1–2.5)
Quartile 4	17/113	1.3 (0.6–3.2)	12/113	3.6 (1.0–14.4)	5/113	0.8 (0.2–3.0)
Test for trend		$P = 0.34$	$P = 0.09$		$P = 0.86$	
Common cut-off						
Points for BMI[b]						
I – Low	17/99	1.0 (referent)	6/99	1.0 (referent)	9/99	1.0 (referent)
II	35/267	1.0 (0.4–2.1)	13/267	1.3 (0.4–4.5)	21/267	1.1 (0.4–2.8)
III	133/376	2.7 (1.3–5.5)	77/376	6.8 (2.2–21.4)	54/376	2.0 (0.8–5.0)
IV – High	103/151	4.5 (2.2–9.5)	59/151	11.3 (3.5–36.4)	41/151	3.4 (1.4–8.7)
Test for trend		$P = 0.001$	$P = 0.001$		$P = 0.001$	

Comparison of the trends in men and women: $P = 0.008$ (oesophageal adenocarcinoma), $P = 0.11$ (lower oesophageal adenocarcinoma), $P = 0.04$ (Oesophago-gastro junction adenocarcinoma). Ψ Data adjusted for age, sex, smoking, and alcohol intake.
a Cut-off points for pre-illness BMI: I – first Quartile (<23.8), II (23.8–25.8), III (25.8–28.7), IV (>28.7).
b Standard cut-off points for BMI I (<22), II, 22–24.9), III (25–29.9), IV (>30).

I, 23.8–25.8 kg/m^2 quartile II, 25.8–28.7 kg/m^2 quartile III, and >28.7 kg/m^2 quartile IV). Forty-five percent of patients with adenocarcinoma of the oesophagus had a pre-illness BMI in the top quartile. For pre-illness BMI, the OR for oesophageal adenocarcinoma rose significantly. When compared to the first quartile, the OR increased from 1.0 (95% CI: 0.6–1.7) for the second, to 1.9 (95% CI: 1.1–3.3) and 3.0 (95% CI: 1.8–5.0) in the third and fourth quartile respectively ($P < 0.001$ for trend). When this analysis was broken down by gender, a significant increase was only observed for men who had an OR of 4.3 (95% CI: 2.3–7.9) for the top quartile versus quartile 1 ($P = 0.001$ for trend) (see Table 1).

The association between pre-illness BMI and the risk of cancer is illustrated in Fig. 2. When looking at oesophageal adenocarcinoma the spline model did not yield a significant improvement in fit, compared to the linear model, for men or women ($P = 0.57$ and $P = 0.38$, respectively). For adenocarcinoma of the lower oesophagus alone, the improved fit was of borderline significance ($P = 0.10$ and $P = 0.07$ for men and women, respectively).

When the heaviest quartile was divided in two (28.7–30.5 kg/m^2 and >30.6 kg/m^2) the pattern became more striking. For males, the OR for oesophageal adenocarcinoma was 6.3 (95%CI: 3.2–21.6) versus the lowest quartile ($P < 0.001$). For adenocarcinoma of the lower oesophagus alone, males with a BMI >30.6 had an OR of 12.9 (95% CI: 4.6–36.6) versus males with a BMI <23.7, $P = 0.001$. Males with a BMI between 28.7 and 30.5 kg/m^{2}had an OR of 5.8 (95% CI: 1.9–17.1) versus males with a BMI <23.7 kg/m^2 ($P = 0.002$ for trend). The odds ratios did not change significantly when patients with a history of gastro-oesophageal reflux disease and Barrett's oesophagus were excluded from the analysis (data not shown).

Analysed by common cut-off points for BMI as defined by the World Health Organisation,[6] the risk of adenocarcinoma of the lower oesophagus was 11.3 for obese men and women (95% CI: 3.5–36.4) versus individuals with a BMI <22 kg/m^2 ($P < 0.001$ for trend). For adenocarcinoma at the oesophago-gastric junction the OR rose significantly with increasing BMI, OR 2.2 (95% CI: 1.2–4.0) for top quartile versus lowest quartile ($P < 0.001$ for trend). When the analysis was broken down by gender, a significant increase was only observed for males who had an OR of 2.9 (95% CI: 1.4–6.1) for top quartile versus lowest quartile ($P < 0.001$ for trend) (see Fig. 3).

Table 2 – Anthropometric indices and risk of gastric cardia adenocarcinoma

Variable	Case-patients/control (n/n)	Multivariate adjusted odds ratio (95% CI)	P value for trend
Pre-illness BMI			
Quartile 1	14/223	1.0 (referent)	P = 0.14
Quartile 2	14/222	0.8 (0.3–2.0)	
Quartile 3	14/225	1.7 (0.7–4.1)	
Quartile 4	22/223	2.3 (1.0–5.3)	
Males only			
Quartile 1	10/74	1.0 (referent)	P = 0.03
Quartile 2	12/96	1.2 (0.4–3.2)	
Quartile 3	11/115	2.0 (0.7–5.7)	
Quartile 4	20/110	3.5 (1.3–9.4)	
Females only			
Quartile 1	4/149	1.0 (referent)	P = 0.70
Quartile 2	2/126	0.3 (0.2–0.3)	
Quartile 3	3/110	1.3 (0.3–6.3)	
Quartile 4	2/113	0.7 (0.1–4.6)	
Common cut-off Points BMI[a]			
I – Low	8/99	1.0 (referent)	P = 0.14
II	14/267	0.9 (0.3–2.7)	
III	25/376	1.4 (0.5–4.1)	
IV – High	17/151	2.7 (0.9–8.0)	

Comparison of the trends in men and women: P = 0.10. Ψ Data adjusted for age, sex, alcohol, smoking.
* Cut-off points for pre-illness BMI: I – first quartile (<23.76), II (23.76–25.84), III (25.84–28.7), IV (>28.7).
a Standard cut-off points for BMI I (<22), II, 22–24.9), III (25–29.9), IV (>30).

Table 3 – Anthropometric indices and risk of gastric adenocarcinoma (non-Cardia)

Variable		Case-patients/control (n/n)	Multivariate adjusted odds ratio (95% CI)	P value for trend
Pre-illness BMI				
Quartile 1		46/223	1.0 (referent)	P = 0.63
Quartile 2		31/222	0.6 (0.3–1.1)	
Quartile 3		37/225	1.0 (0.6–1.7)	
Quartile 4		42/223	0.9 (0.5–1.6)	
Males only				
Quartile 1		26/74	1.0	P = 0.20
Quartile 2		21/96	0.7 (0.3–1.4)	
Quartile 3		24/115	1.0 (0.4–2.1)	
Quartile 4		30/110	1.3 (0.6–2.6)	
Females only				
Quartile 1		20/149	1.0	P = 0.66
Quartile 2		10/126	0.6 (0.3–1.4)	
Quartile 3		13/110	1.1 (0.5–2.5)	
Quartile 4		12/113	0.6 (0.3–1.5)	
Common cut-off Points BMI[a]	I – Low	16/99	1.0 (referent)	P = 0.63
	II	50/267	1.3 (0.6–2.7)	
	III	57/376	1.2 (0.6–2.5)	
	IV – High	33/151	1.5 (0.7–3.2)	

Comparison of the trends in men and women: P = 0.21. Ψ data adjusted for age, sex, alcohol, smoking.
* Cut-off points for pre-illness BMI: I – first quartile (<23.76), II (23.76–25.84), III (25.84–28.7), IV (>28.7).
a Standard cut-off Points for BMI I (<22), II, 22–24.9), III (25–29.9), IV (>30).

3.3. *Adenocarcinoma of gastric cardia*

The median pre-illness BMI for patients who developed adenocarcinoma of the gastric cardia was 26.6 kg/m^2 (IQ 24.3–30.1). This was not significantly heavier than healthy controls, with a median of 25.8 kg/m^2 (IQ 23.8–28.7). Using multivariate logistic regression adjusted for age, gender, smoking, and alcohol, the adjusted odds ratio for cardia adenocarcinoma for males and females together was 2.3 (95% CI: 1.0–5.3) among persons in the highest BMI quartile compared to those in the lowest BMI quartile. This trend was not significant (P = 0.14). When the analysis was repeated for each gender

Table 4 – Anthropometric indices and squamous cell carcinoma

Variable	Case-patients/control (n/n)	Multivariate adjusted odds ratio (95% CI)	P value for trend
Pre-illness BMI[a]			
Males and females			
Quartile 1	116/223	1.0 (referent)	P = 0.001
Quartile 2	59/222	0.5 (0.3–0.8)	
Quartile 3	43/225	0.6 (0.3–0.9)	
Quartile 4	33/223	0.3 (0.2–0.6)	
Males Only			
Quartile 1	45/74	1.0 (referent)	P = 0.1
Quartile 2	38/96	0.8 (0.4–1.6)	
Quartile 3	24/110	0.8 (0.4–1.6)	
Quartile 4	21/110	0.6 (0.3–1.2)	
Females only			
Quartile 1	71/149	1.0 (referent)	P = 0.001
Quartile 2	21/126	0.4 (0.2–0.7)	
Quartile 3	24/110	0.4 (0.2–0.9)	
Quartile 4	21/110	0.2 (0.1–0.4)	
Common cut-off Points BMI[b]			
I – Low	79/99	1.0 (referent)	P = 0.001
II	85/267	0.4 (0.3–0.7)	
III	60/376	0.3 (0.2–0.5)	
IV – High	27/151	0.2 (0.1–0.4)	

Comparison of the trends in men and women: P = 0.02.
Ψ Data adjusted for age, sex, alcohol, smoking.
a Cut-off points for pre-illness BMI: I – first quartile (<23.76), II (23.76–25.84), III (25.84–28.7), IV (>28.7).
b Standard cut-off points for BMI I (<22), II, 20–24.9), III (25–29.9), IV (>30).

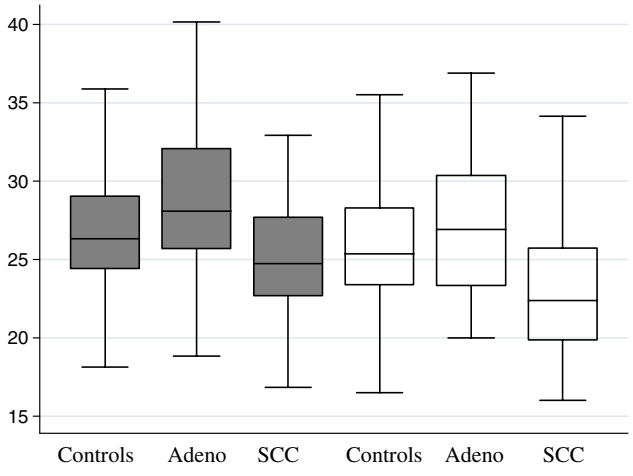

Fig. 1 – Median BMI and (upper and lower quartiles) for males (Black) and females (White) with Adenocarcinoma and SCC versus healthy controls (P < 0.001).

the association with obesity and gastric cardia adenocarcinoma was significant only in men. The OR for males in the top BMI quartile was 3.5 (95%CI: 1.3–9.4) versus males in the lowest BMI quartile (P = 0.03 for trend) (see Table 2).

3.4. *Non-cardia gastric adenocarcinoma*

No relationship between BMI and non-cardia adenocarcinoma of the stomach was observed by either univariate or multivariate analysis. When the analysis was repeated using common cut-off points for BMI the results remained insignificant (see Table 3).

3.5. *Oesophageal squamous cell carcinoma*

Prior to illness 50% of patients with SCC of the oesophagus had a normal BMI, 24% were overweight, 11% obese, and 15% underweight. The median pre-illness BMI for SCC cases was 24 kg/m^2 (IQ: 21.3–26.7 kg/m^2) and this was significantly lower compared with both controls and adenocarcinoma cases ($P < 0.001$) (see Fig. 1). Using multivariate logistic regression analysis, adjusting for age, gender, smoking, alcohol intake, an inverse association between pre-illness BMI and risk of SCC was found ($P < 0.001$) (see Fig. 1). This inverse association was only significant for females. With increasing BMI the OR of SCC fell significantly, with an OR of 0.2 for the top quartile compared with the lowest quartile (95% CI: 0.1–0.4, $P < 0.001$ for trend). A comparison of the trends between males and females showed a significant difference in risk pattern ($P = 0.02$). When the analysis was repeated using common cut-off points for BMI the inverse association remained highly statistically significant (see Table 4).

4. Discussion

This study of an Irish population firmly supports the link between rising BMI and the risk of both adenocarcinoma of the oesophagus and gastric cardia. Obesity (BMI >30 kg/m^2) was associated with a 4-fold risk of adenocarcinoma of the

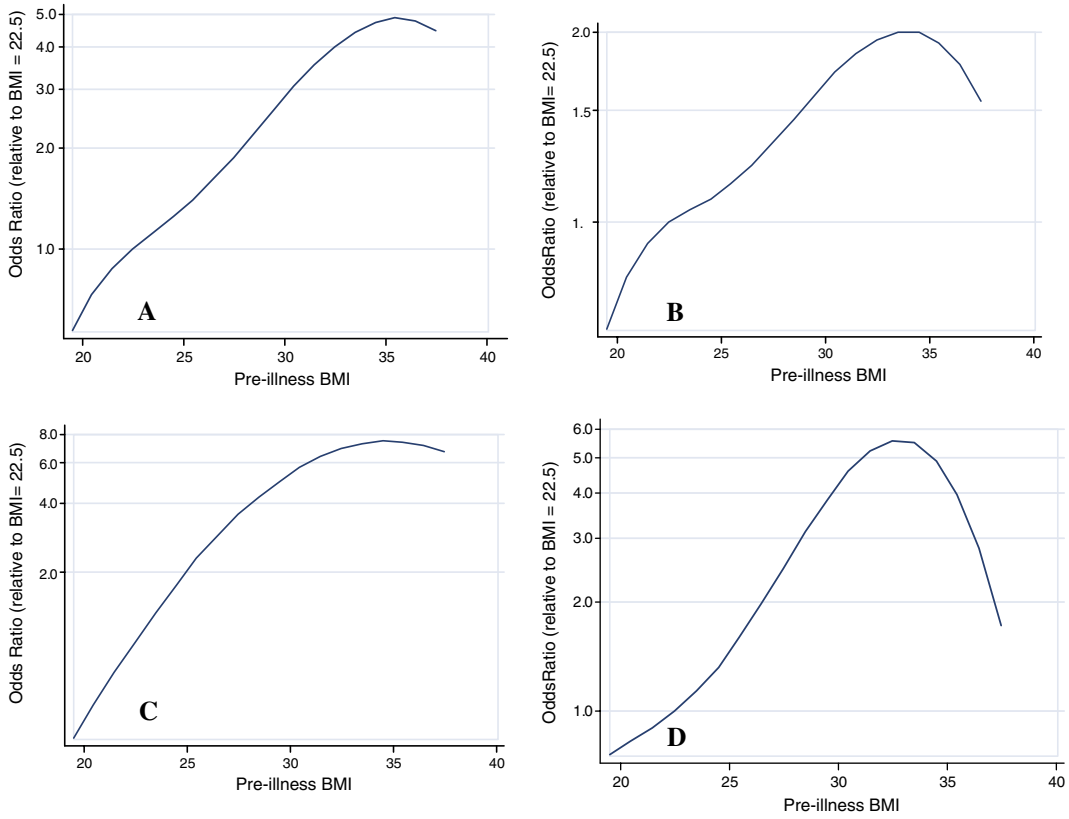

Fig. 2 – Spline curves plotting relationship between pre-illness BMI and risk of oesophageal adenocarcinoma for: (A) males only, (B) oesophageal adenocarcinoma females only, (C) lower oesophageal adenocarcinoma males only, and (D) lower oesophageal adenocarcinoma females only. Odds ratios are relative to a BMI of 22.5.

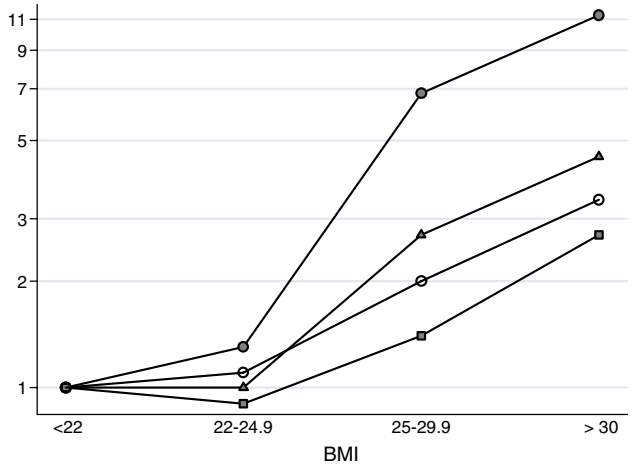

Fig. 3 – Odds ratio for adenocarcinoma of oesophagus (all sites: ▲), lower oesophagus (●), oesophagus gastric junction (○) and gastric cardia (■) for common BMI groups relative to the BMI <22 group. Odds ratios are shown on a log-scale.

oesophagus compared with males and females with a normal BMI. When the analysis was split for individual tumour sites the risks associated with high BMI were strikingly more marked for males compared with females. Males with a BMI in the top quartile had an OR of adenocarcinoma of the lower oesophagus over nine times that of males in the lowest quartile. For females, the OR was 3.6 for the top quartile compared with the lowest quartile but this was not significant. When common cut-off points for BMI[8] were used, individuals with a BMI >30 kg/m^2 had over 11 times increased risk for adenocarcinoma of the lower oesophagus compared with those with a normal BMI. This risk of adenocarcinoma was independent of the presence of reflux symptoms and the presence of Barrett's oesophagus did not affect the strength of the association with BMI. For adenocarcinoma of the oesophago-gastric junction the relationship between obesity and cancer was only significant for males, with the risk being three-fold higher for males in the top quartile versus the lowest quartile.

Several studies report a relationship between obesity and adenocarcinoma of the oesophagus. The first population-based case-control study to investigate dietary and nutritional risk factors for adenocarcinoma of the oesophagus was carried out by Brown and colleagues[9] in 1995: 174 males with ACA and 750 control subjects were studied from 1985 to 1989, and they reported an increased risk (OR 3.1) in the heaviest quartile compared with the lightest quartile. Vaughan and colleagues,[10] in a case-control study of 404 cases of oesophageal cancer (298 adenocarcinoma and 106 SCC) and 724 healthy controls, reported that patients in the highest decile of BMI had the greatest (OR 1.9) risk of adenocarcinoma. Another study, by Chow and colleagues[11] examined anthropometric risk factors in a population-based case-control study of 589 cases of SCC and 554 adenocarcinoma cases, along with 695 healthy control subjects. The risk of adenocar-

cinoma only rose with increasing BMI, and the magnitude of the association was greatest amongst the younger age groups and amongst non-smokers. Lagergren and colleagues[12] conducted a nationwide, population-based case-control study in Sweden of 189 cases of adenocarcinoma of the oesophagus, 262 cases of gastric cardia adenocarcinoma, 167 of SCC of the oesophagus, and 820 controls, and reported a significant dose-dependent relationship between BMI and oesophageal adenocarcinoma. The adjusted OR was 7.6 among persons in the highest BMI quartile compared to persons in the lowest quartile. In the UK, Cheng and colleagues[13] conducted a case-control study of 74 women with adenocarcinoma of the oesophagus and showed that a high BMI at the age of 20 years and low consumption of fruit was associated with increased risk (OR 6.04 for highest BMI quartile versus lowest). A recent study by Engeland and colleagues[14] reported on 2245 cases of oesophageal cancer from Norway. This study did not control for smoking, alcohol intake or diet, but again reported that obese men had a relative risk of death from adenocarcinoma of the oesophagus 2.58 times that of normal weight men.

The present study demonstrates a strikingly greater link between BMI and adenocarcinoma of the oesophagus or cardia in men compared with women. An explanation for this is unclear. One possible mechanism links the gender-specific different patterns of adipose tissue distribution between males and females, and the well-described association of chronic gastro-oesophageal reflux disease (GORD) and adenocarcinoma. Males deposit fat preferentially in the intra-abdominal region at all ages in contrast to females who deposit sub-cutaneous adipose tissue predominantly in youth, and only post-middle age do females tend to deposit intra-abdominal adipose tissue preferentially.[16] This central or android adiposity may increase GORD.[17,18] Obese subjects compared with non-obese subjects have elevated intra-abdominal and intra-gastric pressures, an increase of transient relaxations of the lower oesophageal sphincter, slower oesophageal transit and abnormal diaphragmatic pinchcock and phreno-oesophageal membrane anatomy.[19] Obese individuals are over four times more likely than lean individuals to have a hiatus hernia (HH), and have an overall prevalence of HH of 40% versus 12.6% for the general population.[20] The central adiposity of obese men may be associated with the risk of neoplastic progression in Barrett's oesophagus and may account for the male predominance of Barrett's oesophagus and adenocarcinoma.[21] With increasing duration and severity of reflux symptoms, and with increasing BMI, the risk of adenocarcinoma increases in a dose dependant manner.[12] When combined, reflux symptoms and obesity entails a relative risk exceeding 100 compared with persons with neither reflux symptoms nor obesity.[22]

This mechanical thesis may be plausible, but since Calle and colleagues[15] highlighted the link between obesity and death rates from not only oesophageal but many cancer types, other mechanisms are likely to be relevant. The pleiotropic properties of the adipocyte have come under scrutiny, in particular adipocytes deposited centrally, more typical of males, as these cells may have endocrine, paracrine and immunological properties. This may be manifested in the metabolic syndrome which is a constellation of metabolic risk factors consisting of atherogenic dyslipidaemia, elevated blood pressure, elevated blood glucose associated with insulin resistance, prothrombic and proinflammatory state. Adipose tissue is a complex and highly active metabolic and endocrine organ, expressing and secreting several endocrine hormones such as leptin, adiponectin, cytokines, complement components, plasminogen-activator inhibitor-1, proteins of the rennin–angiotensin system and resistin. It is also a major site for the metabolism of sex steroids and glucocorticoids.[22] The important endocrine function of adipose tissue is emphasised by adverse metabolic consequences of adipose tissue excess. In the metabolic syndrome insulin resistance induces compensatory hyper-insulinaemia with increased insulin-like growth factor-1 (IGF-1 production), sex hormones and unbound sex hormone level, and these may interfere with cellular differentiation, proliferation and apoptosis thus increasing the risk of pre-neoplastic and neoplastic cell growth.[23] Leptin, a protein produced by adipose tissue has recently been shown to increase proliferation of several cancer cell lines in vitro[24] and further studies are required relating adipocyte function with cancer biology. Why certain tumours could be promoted by the endocrine properties of adipocytes demands further study, in particular whether leptin and other growth factor receptors are differentially expressed in Barrett's and oesophageal adenocarcinoma compared with squamous epithelium.

The authors recognise that this study, like most comparable studies, used pre-illness reported weights, and recall bias is possible. The link however between body mass and cancer risk was unknown to the patients, and the patients were unaware of the histological subtype of their tumours, and thus any impact of recall bias should be similar for SCC and adenocarcinoma. Moreover, other studies indicate that overweight and obese individuals under-report their weight to a greater extent than lean individuals, and that BMI from self-reported weights underestimates the true prevalence of overweight and obesity.[25,26] If this assumption is accepted, we can have confidence in the prevalence of obesity reported in this study and it may even understate the association.

In conclusion, Body Mass Index and adenocarcinoma of the oesophagus and gastric cardia are directly related in an Irish population. Males are especially sensitive to the increased risk of this cancer posed by obesity. The prevalence of obesity in Ireland and in Western countries could be important in understanding the increasing incidence of this tumour. Further research into oesophageal and gastric cardia adenocarcinoma is needed to clarify the risk factors and mechanisms responsible for the upward trends as well as the racial and gender disparities. Further work should establish the link between obesity, reflux, and oesophageal adenocarcinoma, and, in particular, the potential pro-inflammatory and pro-tumourigenic pathways facilitated through the altered immunological, metabolic and endocrine milieu in obesity, in particular male obesity.

Conflict of interest statement

None declared.

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