

# Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus

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Revised 22 July 2007  
Accepted 7 August 2007  
Published Online First  
11 October 2007

## ABSTRACT

**Objective:** To measure the relative risks of adenocarcinomas of the oesophagus and gastro-oesophageal junction associated with measures of obesity, and their interactions with age, sex, gastro-oesophageal reflux symptoms and smoking.

**Design and setting:** Population-based case-control study in Australia.

**Patients:** Patients with adenocarcinomas of the oesophagus ( $n = 367$ ) or gastro-oesophageal junction ( $n = 426$ ) were compared with control participants ( $n = 1580$ ) sampled from a population register.

**Main outcome measure:** Relative risk of adenocarcinoma of the oesophagus or gastro-oesophageal junction.

**Results:** Risks of oesophageal adenocarcinoma increased monotonically with body mass index (BMI) ( $p_{\text{trend}} < 0.001$ ). Highest risks were seen for BMI  $\geq 40$  kg/m<sup>2</sup> (odds ratio (OR) = 6.1, 95% CI 2.7 to 13.6) compared with "healthy" BMI (18.5–24.9 kg/m<sup>2</sup>). Adjustment for gastro-oesophageal reflux and other factors modestly attenuated risks. Risks associated with obesity were substantially higher among men (OR = 2.6, 95% CI 1.8 to 3.9) than women (OR = 1.4, 95% CI 0.5 to 3.5), and among those aged  $< 50$  years (OR = 7.5, 95% CI 1.7 to 33.0) than those aged  $\geq 50$  years (OR = 2.2, 95% CI 1.5 to 3.1). Obese people with frequent symptoms of gastro-oesophageal reflux had significantly higher risks (OR = 16.5, 95% CI 8.9 to 30.6) than people with obesity but no reflux (OR = 2.2, 95% CI 1.1 to 4.3) or reflux but no obesity (OR = 5.6, 95% CI 2.8 to 11.3), consistent with a synergistic interaction between these factors. Similar associations, but of smaller magnitude, were seen for gastro-oesophageal junction adenocarcinomas.

**Conclusions:** Obesity increases the risk of oesophageal adenocarcinoma independently of other factors, particularly among men. From a clinical perspective, these data suggest that patients with obesity and frequent symptoms of gastro-oesophageal reflux are at especially increased risk of adenocarcinoma.

The incidence of adenocarcinomas of the oesophagus and the gastro-oesophageal junction has been rising in many countries,<sup>1–4</sup> in some populations faster than for any other major cancer.<sup>5</sup> In contrast, the incidence of oesophageal squamous cell carcinoma (SCC) has remained stable or even declined in the same populations over the same periods. Such widespread changes in occurrence imply a profound shift in the prevalence of causal exposures, given no equivalent systematic changes in detection or diagnosis.<sup>5</sup>

Epidemiological studies strongly implicate gastro-oesophageal reflux as the primary causal factor for oesophageal adenocarcinoma<sup>6–7</sup> and, to a lesser

extent, adenocarcinomas of the gastro-oesophageal junction. Obesity and overweight are associated with an increased prevalence of gastro-oesophageal reflux symptoms,<sup>8–14</sup> and thus gastro-oesophageal reflux has been widely (although not universally<sup>15</sup>) assumed to explain the observed increase in risk of oesophageal adenocarcinoma associated with higher levels of body mass.<sup>16–20</sup> However, obesity has been linked with markedly increased risks of other cancers,<sup>21–22</sup> and thus there are plausible grounds for speculating that high levels of body fat may promote carcinogenesis through other pathways.<sup>23</sup> These alternative causal hypotheses remain largely untested for oesophageal cancers.

Here, we report the findings of a large population-based case-control study evaluating the effects of obesity on the risk of adenocarcinomas of the oesophagus and gastro-oesophageal junction, alone and in combination with other causal factors.

## PATIENTS AND METHODS

Approval to undertake the study was obtained from the research ethics committees of the Queensland Institute of Medical Research and participating hospitals. We obtained written informed consent from case patients and control participants to take part.

### Study participants

Patients eligible for inclusion were those people aged 18–79 years with a histologically confirmed primary invasive adenocarcinoma or squamous cell carcinoma of the oesophagus or gastro-oesophageal junction diagnosed from 1 July 2001 (in Queensland) or 1 July 2002 (in the other mainland states of Australia) until 30 June 2005. The principal mode of ascertainment was via major treatment centres throughout Australia; those missed at these centres were identified by state-based cancer registries (notification of cancer diagnosis is mandatory in all states of Australia).

We identified 1610 eligible patients with a primary diagnosis of oesophageal cancer attending treatment centres during the study period. Of these, doctors refused contact with 71 patients and 167 died before consent could be obtained. A further 181 patients were excluded because they were too ill (91), mentally incapable (23), could not read or write in English (41) or were uncontactable (26). The remaining 1191 patients were invited to participate, and of these, 928 (78% of those invited) agreed to take part.

**Table 1** Characteristics of study participants

		Controls		Adenocarcinoma of the oesophagus		Adenocarcinoma of the gastro-oesophageal junction	
		Men	Women	Men	Women	Men	Women
		(n = 1040)	(n = 540)	(n = 330)	(n = 37)	(n = 370)	(n = 56)
Age	Mean (SD)	62.5 (10.5)	56.7 (12.8)	63.5 (9.3)	65.6 (11.9)	63.6 (9.6)	61.8 (10.5)
Educational level (%)	School	35.9	50.6	43.6	64.9	37.3	58.9
	Trade	29.1	10.0	29.1	18.9	28.4	14.3
	Diploma	18.4	25.9	20.0	13.5	22.7	19.6
	Degree	16.4	13.3	6.7	2.7	11.1	7.1
	Not stated	0.3	0.2	0.6	0	0.5	0
BMI last year	Mean (SD)	26.9 (4.2)	26.9 (5.7)	29.1 (5.0)	29.6 (8.3)	28.3 (4.7)	28.8 (6.1)
Maximum BMI	Mean (SD)	28.5 (4.6)	28.7 (6.1)	30.8 (5.0)	32.1 (8.5)	29.8 (4.7)	31.3 (7.1)
BMI age 20 years	Mean (SD)	23.0 (3.3)	21.6 (3.4)	23.9 (3.6)	22.5 (3.5)	23.6 (3.1)	23.0 (3.7)
Smoking status	Never smoker	37.2	59.8	23.9	40.5	20.8	35.7
	Quit >20 years	28.1	13.7	25.2	16.2	28.4	14.3
	Quit 1–20 years	19.8	12.6	31.2	16.2	23.5	17.9
	Current	13.1	13.3	19.1	27.0	26.5	32.1
Cumulative smoking history (pack-years)	Never smoker	37.2	59.8	23.9	40.5	20.8	35.7
	1–14	25.2	24.6	20.0	18.9	20.0	21.4
	15–29	15.0	9.4	19.1	16.2	22.7	17.9
	30–49	13.2	3.7	22.4	16.2	22.4	23.2
	50+	9.4	2.4	14.6	8.1	14.0	1.8
Frequency of reflux symptoms 10 years ago	Never	42.1	48.2	21.5	29.7	27.0	35.7
	<Weekly	45.1	40.2	36.4	21.6	35.7	32.1
	≥Weekly	11.9	11.3	41.5	43.2	36.8	30.4
	Never drinker	9.5	25.7	7.3	24.3	6.8	25.0
Mean alcohol consumption (10 g alcohol units/week)	<1 Drink/week	1.5	5.7	2.4	0	0.8	5.4
	1–6 Drinks/week	24.6	44.4	19.4	56.8	25.7	44.6
	7–20 Drinks/week	36.8	21.5	37.3	18.9	36.2	23.2
	21+ Drinks/week	27.5	2.6	33.3	0	30.5	1.8
Frequency of aspirin use	Never	39.2	53.0	45.2	62.1	45.1	44.6
	Occasional	40.5	34.6	33.6	27.0	34.3	33.9
	<Weekly	4.5	2.8	6.1	2.7	3.8	7.1
	≥Weekly	15.6	9.3	14.2	8.1	15.7	14.3

Column percentages may not sum to 100% owing to rounding and missing values.

A further 739 alive and eligible patients were identified by the cancer registries (835 potentially eligible patients died before being identified by the cancer registries), and of these, treating doctors refused contact for 84 patients, 37 patients were incapable of taking part and 232 patients were unable to be contacted. The remaining 386 cancer registry patients were invited to take part, of whom 253 agreed (66% of those invited). Thus, a total of 1181 patients with oesophageal cancer consented to take part in the study (928 clinic patients and 253 registry patients). Questionnaires were returned by 1102 patients (367 and 426 with adenocarcinomas of the oesophagus and gastro-oesophageal junction respectively, and 309 patients with SCC).

Potential controls were randomly selected from the Australian Electoral Roll (enrolment is compulsory). We prospectively sampled controls from within strata of age (in 5-year age groups) and state of residence to match the distribution of the case series. We aimed for similar numbers of male cases and controls in each stratum of age and state; female controls were intentionally oversampled at all ages to accommodate their simultaneous enrolment in a parallel case-control study of ovarian cancer.<sup>24</sup>

Of 3258 potentially eligible control participants, 41 could not be contacted and 175 were excluded because they had died (16), were too ill (61), or unable to read or write in English (98). Of 3042 controls meeting the inclusion criteria, 1680 (55%) gave

their consent to take part. Completed questionnaires were returned by 1580 controls (48% of all potentially eligible controls selected from the roll).

**Data collection**

Data were collected from all participants through self-completed, mailed questionnaires. This was followed by a telephone interview to record detailed information about past use of drugs, as well as to clarify issues arising from the self-completed questionnaires, as needed. The questionnaire elicited information about social background (education, occupation, income), as well as height and weight 1 year ago (1 year before diagnosis for cases), maximum ever weight and weight at age 20 years. We calculated the body mass index (BMI) by dividing weight in kilograms by the square of height in metres. Standard BMI categories were used for analysis (<18.5 kg/m<sup>2</sup>, “underweight”; 18.5–24.9 kg/m<sup>2</sup>, “healthy weight”; 25–29.9 kg/m<sup>2</sup>, “overweight”; 30–34.9 kg/m<sup>2</sup>, “obese I”, 35–39.9 kg/m<sup>2</sup> “obese II” and ≥40 kg/m<sup>2</sup> “obese III”).

Participants were asked whether, over their whole life, they had ever smoked more than 100 cigarettes, cigars, or pipes; positive responses elicited further questions about ages starting and stopping smoking and typical daily consumption. We derived the number of pack-years of tobacco exposure by dividing the number of cigarettes smoked daily by 20 and

**Table 2** Relative risk for adenocarcinomas of the oesophagus and gastro-oesophageal junction associated with measures of body mass index (BMI) at different time points

	Oesophageal adenocarcinoma			Gastro-oesophageal junction adenocarcinoma		
	Controls/Cases	Fully adjusted, except reflux* OR (95% CI)	Fully adjusted, with reflux† OR (95% CI)	Cases	Fully adjusted, except reflux† OR (95% CI)	Fully adjusted, with reflux OR (95% CI)
<b>BMI last year (kg/m<sup>2</sup>)</b>						
<18.5	21/1	0.3 (0.0 to 2.6)	0.5 (0.1 to 3.6)	1	0.2 (0.0 to 1.7)	0.3 (0.0 to 2.0)
18.5–24.9	528/71	1.0 (ref)	1.0 (ref)	107	1.0 (ref)	1.0 (ref)
25.0–29.9	650/150	1.4 (1.0 to 1.9)	1.2 (0.9 to 1.7)	168	1.1 (0.8 to 1.4)	1.0 (0.7 to 1.3)
30.0–34.9	222/89	2.7 (1.8 to 3.9)	2.1 (1.4 to 3.1)	98	1.9 (1.3 to 2.6)	1.6 (1.1 to 2.2)
35.0–39.9	68/25	3.1 (1.8 to 5.5)	2.5 (1.4 to 4.4)	27	2.0 (1.2 to 3.4)	1.7 (1.0 to 3.0)
40+	24/16	7.0 (3.3 to 15.0)	6.1 (2.7 to 13.6)	9	2.6 (1.1 to 6.2)	2.4 (1.0 to 5.8)
p trend		<0.001	<0.001		<0.001	<0.001
<b>BMI maximum (kg/m<sup>2</sup>)</b>						
<18.5	9/1	0.9 (0.1 to 8.7)	1.4 (0.2 to 11.9)	0	–	–
18.5–24.9	356/39	1.0 (ref)	1.0 (ref)	55	1.0 (ref)	1.0 (ref)
25.0–29.9	708/136	1.4 (0.9 to 2.0)	1.2 (0.8 to 1.7)	178	1.3 (0.9 to 1.8)	1.1 (0.8 to 1.6)
30.0–34.9	333/114	2.5 (1.6 to 3.7)	1.9 (1.3 to 3.0)	122	1.9 (1.3 to 2.7)	1.6 (1.1 to 2.4)
35.0–39.9	107/43	4.1 (2.4 to 6.8)	3.1 (1.8 to 5.3)	47	2.9 (1.8 to 4.6)	2.4 (1.5 to 3.9)
40+	52/24	5.2 (2.7 to 9.9)	4.4 (2.3 to 8.7)	15	2.1 (1.1 to 4.2)	1.9 (1.0 to 3.8)
p trend		<0.001	<0.001		<0.001	<0.001
<b>BMI age 20 years (kg/m<sup>2</sup>)</b>						
<18.5	121/14	0.8 (0.4 to 1.4)	0.8 (0.5 to 1.6)	9	0.4 (0.2 to 0.8)	0.4 (0.2 to 0.8)
18.5–24.9	1144/227	1.0 (ref)	1.0 (ref)	282	1.0 (ref)	1.0 (ref)
25.0–29.9	237/81	1.7 (1.2 to 2.3)	1.7 (1.2 to 2.3)	97	1.6 (1.2 to 2.1)	1.6 (1.2 to 2.2)
30.0–34.9	29/13	2.6 (1.3 to 5.2)	2.4 (1.1 to 5.1)	13	2.1 (1.0 to 4.1)	2.0 (0.9 to 4.1)
35.0+	6/5	3.6 (1.0 to 13.0)	2.9 (0.8 to 11.2)	2	1.1 (0.2 to 5.9)	1.0 (0.2 to 5.3)
p trend		<0.001	<0.001		<0.001	<0.001
<b>Change in BMI (kg/m<sup>2</sup>)</b>						
<3	581/98	1.0 (ref)	1.0 (ref)	131	1.0 (ref)	1.0 (ref)
3–4.9	338/73	1.2 (0.9 to 1.7)	1.0 (0.7 to 1.5)	96	1.1 (0.8 to 1.6)	1.0 (0.7 to 1.4)
5–9.9	406/117	1.7 (1.3 to 2.4)	1.4 (1.0 to 2.0)	115	1.2 (0.9 to 1.6)	1.1 (0.8 to 1.5)
10+	153/47	2.2 (1.4 to 3.4)	1.8 (1.2 to 2.8)	50	1.6 (1.0 to 2.3)	1.4 (0.9 to 2.1)
p trend		<0.001	0.002		0.05	0.26

\*Adjusted for age, sex, state, household income, cumulative smoking history, mean alcohol consumption and frequency of aspirin use in the 5 years before diagnosis.

†Adjusted for above factors and frequency of gastro-oesophageal reflux symptoms 10 years before diagnosis.

multiplying by the total number of years smoked. For analysis, “never smokers” were the reference category and “ever smokers” were categorised according to total pack-years of smoking.

We asked participants to report the frequency with which they consumed different classes of alcohol (low-alcohol beer, regular beer, white wine, red wine, port/sherry and spirits/liqueurs) between ages 20–29, 30–49 and ≥50 years, as applicable. Total alcohol consumption was summed across all age groups for all types of alcohol, from which we calculated a weighted average number of standard drinks (10 g ethanol) consumed each week between age 20 years and current age.

We assessed the frequency of symptoms of gastro-oesophageal reflux 10 years before diagnosis, defined as the presence of heartburn (“a burning pain behind the breastbone after eating”) or acid reflux (“a sour taste from acid or bile rising up into the mouth or throat”). For analysis, we used the highest reported frequency for either symptom and defined “frequent symptoms” as those occurring at least weekly.<sup>9, 10</sup> Frequency of aspirin intake during the past 5 years was ascertained on a scale ranging from “never” to “two or more times/day”.

Details of the histological type and anatomical site of each tumour were abstracted from diagnostic pathology reports. Anatomical sites of tumours were categorised according to the WHO classification<sup>25</sup> into “oesophageal” and “gastro-oesophageal junction” tumours.

### Statistical analyses

We calculated the odds ratio (OR) and 95% confidence interval (95% CI) associated with each exposure using multivariable logistic regression analysis in SAS version 9.1 (SAS Institute, Inc, Cary NC, USA). Statistical significance was determined at  $\alpha = 0.05$ , and all tests for statistical significance were two sided. Our approach was first, to fit minimally adjusted models which contained terms for each exposure and the matching variables (sex, age and state). We then estimated relative risks associated with BMI adjusted for these variables and income, smoking, alcohol consumption and frequency of aspirin use. Finally, we fitted fully adjusted models which included the preceding variables as well as a term for frequency of gastro-oesophageal reflux symptoms. For each variable, the lowest category was the reference category, except for BMI for which the reference was the healthy weight range. We tested for trend by including each category as an ordinal variable in the multivariable model, with category values taken as the midpoint of the range. For variables in which the lowest category was “unexposed” (eg, pack-years of smoking), trend tests were restricted to the “exposed” categories.

To assess potential interactions between BMI and reflux or smoking, we created new variables that reclassified participants according to their combined exposure to BMI and the other factors. Risks for each category of combined exposure were estimated relative to the reference category in multivariable

**Table 3** Relative risks for adenocarcinomas of the oesophagus and gastro-oesophageal junction associated with body mass index in the year before diagnosis, stratified by sex and age

BMI	Controls/cases	Oesophageal adenocarcinoma		Gastro-oesophageal junction adenocarcinoma		
		Fully adjusted, except reflux*	Fully adjusted, with reflux†	Cases	Fully adjusted, except reflux	Fully adjusted, with reflux
		OR (95% CI)	OR (95% CI)		OR (95% CI)	OR (95% CI)
<b>Women</b>						
<25.0	224/12	1.0 (ref)	1.0 (ref)	16	1.0 (ref)	1.0 (ref)
25.0–29.9	166/8	0.5 (0.2 to 1.5)	0.5 (0.2 to 1.5)	18	1.0 (0.6 to 2.7)	1.2 (0.5 to 2.5)
≥30.0	125/13	1.7 (0.7 to 4.1)	1.4 (0.5 to 3.5)	22	2.3 (1.1 to 4.7)	1.9 (0.9 to 4.1)
<b>Men</b>						
<25.0	325/60	1.0 (ref)	1.0 (ref)	92	1.0 (ref)	1.0 (ref)
25.0–29.9	484/142	1.6 (1.1 to 2.2)	1.3 (0.9 to 1.9)	150	1.1 (0.8 to 1.5)	1.0 (0.7 to 1.4)
≥30.0	189/117	3.3 (2.3 to 4.8)	2.6 (1.8 to 3.9)	112	2.1 (1.5 to 2.9)	1.7 (1.2 to 2.5)
<b>Age &lt;50 years</b>						
<25.0	127/5	1.0 (ref)	1.0 (ref)	9	1.0 (ref)	1.0 (ref)
25.0–29.9	94/10	1.8 (0.5 to 6.7)	1.4 (0.3 to 5.5)	20	1.8 (0.7 to 4.7)	1.3 (0.5 to 3.8)
≥30.0	49/14	10.5 (2.7 to 40.9)	7.5 (1.7 to 33.0)	14	3.9 (1.3 to 11.6)	3.5 (1.1 to 11.4)
<b>Age ≥50 years</b>						
<25.0	422/67	1.0 (ref)	1.0 (ref)	99	1.0 (ref)	1.0 (ref)
25.0–29.9	556/140	1.4 (1.0 to 2.0)	1.2 (0.9 to 1.7)	148	1.1 (0.8 to 1.5)	1.0 (0.7 to 1.3)
≥30.0	265/116	2.8 (1.9 to 3.9)	2.2 (1.5 to 3.1)	120	1.9 (1.4 to 2.7)	1.6 (1.2 to 2.3)

\*Adjusted for age (in years), sex, state of residence, household income, cumulative smoking history, mean alcohol consumption and frequency of aspirin use in the 5 years before diagnosis.

†Adjusted for above factors and frequency of gastro-oesophageal reflux symptoms 10 years before diagnosis.

logistic regression analyses. To quantify biological interaction, we calculated the synergy index  $S^{26}$  using the algorithm of Andersson.<sup>27</sup>

**RESULTS**

Table 1 presents the distribution of salient characteristics of cases and controls. Female controls were younger on average than female case patients owing to their simultaneous sampling for a related study of ovarian cancer.

**BMI and risk of adenocarcinoma of the oesophagus**

In multivariable models adjusting for age, sex, income, smoking, alcohol and aspirin consumption, we found that people who were overweight had modestly increased risks of oesophageal adenocarcinoma compared with the reference category, and risks increased with increasing BMI ( $p_{trend} < 0.001$ ). Severely obese people (BMI  $\geq 40$  kg/m<sup>2</sup>) had a sevenfold increased risk of adenocarcinoma compared with people in the healthy weight range. Further adjustment for symptoms of reflux attenuated the association only modestly, and relative risks for the severely obese category remained very high (table 2). Collapsing the three obese categories into a single group (ie, BMI  $\geq 30$  kg/m<sup>2</sup>) yielded a crude risk estimate of 3.3 (95% CI 2.3 to 4.6) which reduced to 2.4 (95% CI 1.7 to 3.5) after full adjustment.

Patterns of risk associated with maximum ever BMI were similar to those seen for BMI in the year before diagnosis. Fully adjusting for confounding factors reduced the risk estimates somewhat; however, significant, dose-dependent associations with BMI persisted ( $p_{trend} < 0.001$ ). At age 20 years, the distribution of BMI was narrow with fewer than 20% of controls reportedly overweight or obese. Nevertheless, we observed significant trends of increasing risk with successively higher BMI categories at this age group, even after fully adjusting for other factors (table 2).

Weight gain during adulthood was associated with modestly increased risks of oesophageal adenocarcinoma, although this was statistically significant only for marked increases in BMI

(>5 kg/m<sup>2</sup>) after adjusting for confounding factors (table 2). As the magnitude of the effect for BMI in the year before diagnosis was largest and remained highly significant after adjusting for the other BMI terms, we used this measure for subsequent analyses.

**BMI and risk of adenocarcinoma of the gastro-oesophageal junction**

Significant trends of increasing risk of adenocarcinoma of the gastro-oesophageal junction with increasing BMI were seen, although the overall magnitude of risks was substantially lower than for oesophageal adenocarcinomas (table 2), and this approached statistical significance for measures of BMI in the year before diagnosis ( $p = 0.080$ ) and maximum ever BMI ( $p = 0.075$ ). Again, adjusting for gastro-oesophageal reflux and other factors led to modest attenuation of effects. Large increases in weight gain since age 20 years were associated with non-significantly increased risks of gastro-oesophageal adenocarcinoma.

**Effects of sex and age**

In stratified analyses, the risks of oesophageal adenocarcinoma associated with BMI were higher among men than women, and were higher among those aged <50 years than those aged  $\geq 50$  years (table 3). Similar patterns of effect modification were seen for gastro-oesophageal junction adenocarcinomas.

**Combined effects of obesity and gastro-oesophageal reflux**

Risks of oesophageal adenocarcinoma increased with increasing frequency of reflux symptoms (“Overall association”, table 4). After reclassifying participants according to their BMI category (“healthy”, “overweight” or “obese”) combined with their reflux symptoms frequency (“none”, “less than weekly”, “at least weekly”), we observed stepwise increases in the risk of oesophageal adenocarcinoma with increasing BMI among those with no reflux symptoms (table 4). Similarly, risks of oesophageal adenocarcinoma increased steadily with reflux

**Table 4** Relative risks for adenocarcinomas of the oesophagus and gastro-oesophageal junction associated with symptoms of gastro-oesophageal reflux or smoking, overall and combined with body mass index (BMI) category

Frequency of reflux	Reflux overall association		Reflux combined with BMI					
	OR*		BMI <25		BMI 25–24.9		BMI ≥30	
	Controls/cases	OR (95% CI)	Controls/cases	OR† (95% CI)	Controls/cases	OR (95% CI)	Controls/cases	OR (95% CI)
Adenocarcinoma oesophagus								
Never	698/82	1.0 (ref)	279/22	1.0 (ref)	253/36	1.6 (0.9 to 2.8)	122/20	2.2 (1.1 to 4.3)
<Weekly	686/128	1.5 (1.1 to 2.0)	218/26	1.4 (0.8 to 2.7)	320/53	1.8 (1.1 to 3.2)	143/46	3.9 (2.2 to 7.0)
≥Weekly	184/153	6.4 (4.5 to 9.0)	52/24	5.6 (2.8 to 11.3)	77/59	7.4 (4.1 to 13.5)	49/64	16.5 (8.9 to 30.6)
Adenocarcinoma gastro-oesophageal junction								
Never	698/120	1.0 (ref)	279/38	1.0 (ref)	253/36	0.8 (0.5 to 1.4)	122/40	2.1 (1.3 to 3.6)
<Weekly	686/150	1.1 (0.9 to 1.5)	218/40	1.2 (0.7 to 1.9)	320/58	1.0 (0.7 to 1.7)	143/47	1.9 (1.2 to 3.2)
≥Weekly	184/153	4.5 (3.3 to 6.1)	52/28	3.6 (2.0 to 6.7)	77/74	5.5 (3.3 to 8.9)	49/47	5.8 (3.3 to 10.1)

Smoking history	Smoking overall association		Smoking combined with BMI					
	OR (95% CI)		BMI <25		BMI 25–24.9		BMI ≥30	
	Controls/cases	OR (95% CI)	Controls/cases	OR‡ (95% CI)	Controls/cases	OR (95% CI)	Controls/cases	OR (95% CI)
Adenocarcinoma oesophagus								
Never smoker	710/94	1.0 (ref)	277/22	1.0 (ref)	274/35	1.2 (0.7 to 2.3)	127/34	3.5 (1.9 to 6.6)
1–29 Pack-years	602/142	1.4 (1.0 to 2.0)	185/19	1.2 (0.6 to 2.4)	272/63	2.0 (1.1 to 3.5)	117/56	3.8 (2.1 to 6.9)
30+ Pack-years	268/131	2.3 (1.6 to 3.3)	87/31	3.0 (1.5 to 5.8)	104/52	3.5 (1.9 to 6.5)	70/40	3.8 (2.0 to 7.4)
Adenocarcinoma gastro-oesophageal junction								
Never smoker	710/97	1.0 (ref)	277/34	1.0 (ref)	274/33	0.9 (0.5 to 1.6)	127/25	1.9 (1.1 to 3.5)
1–29 Pack-years	602/180	2.1 (1.5 to 2.8)	185/35	1.8 (1.0 to 3.1)	272/82	2.0 (1.2 to 3.2)	117/58	3.6 (2.2 to 6.1)
30+ Pack-years	268/149	3.2 (2.3 to 4.6)	87/39	3.2 (1.8 to 5.8)	104/53	3.1 (1.8 to 5.4)	70/51	4.6 (2.6 to 8.1)

\*Odds ratio and 95% confidence interval adjusted for age (in years), sex, income, state of residence, cumulative smoking history, alcohol consumption, frequency of aspirin use in the past 5 years, frequency of gastro-oesophageal reflux symptoms 10 years before diagnosis and BMI in the year before diagnosis.

†Odds ratio and 95% confidence interval adjusted for age (in years), sex, income, state of residence, cumulative smoking history, alcohol consumption and frequency of aspirin use in the past 5 years.

‡Odds ratio adjusted for age (in years), sex, income, state of residence, frequency of gastro-oesophageal reflux symptoms 10 years before diagnosis, alcohol consumption and frequency of aspirin use in the past 5 years.

frequency among those in the “healthy” BMI range. People in the highest combined exposure category (ie, BMI ≥30.0 with at least weekly symptoms of reflux) had significantly higher risks of oesophageal adenocarcinoma than people with only one of these conditions. Risks of combined exposure were almost threefold higher than expected assuming additive interactions ( $S = 2.7$ , 95% CI 1.3 to 5.4).

Risks of gastro-oesophageal junction adenocarcinomas were also substantially higher for obese people than those in the healthy weight range at each level of reflux frequency. The co-occurrence of obesity and frequent reflux symptoms (OR = 5.8, 95% CI 3.3 to 10.1) led to considerably higher risks than either obesity in the absence of reflux (OR = 2.1, 95% CI 1.3 to 3.6) or reflux in the absence of obesity (OR = 3.6, 95% CI 2.0 to 6.7), but the risks were not significantly different from those expected assuming additive effects ( $S = 1.3$ , 95% CI 0.6 to 2.7).

### Combined effects of obesity and smoking

Smokers with high cumulative exposures had significantly higher risks of oesophageal and gastro-oesophageal junction adenocarcinomas than never smokers (table 4, “Smoking overall association”). Analysis of smoking status (never, former, current) resulted in associations of similar magnitude (oesophageal adenocarcinoma: former smokers OR = 1.5, 95% CI 1.1 to 2.1; current smokers OR = 2.3, 95% CI 1.5 to 3.5; gastro-oesophageal adenocarcinoma: former smokers OR = 1.9, 95% CI 1.4 to 2.6; current smokers OR = 4.3, 95% CI 3.0 to 6.1). For

adenocarcinomas of the oesophagus, risk estimates for cumulative smoking history were only minimally attenuated after further adjusting for smoking status, whereas for adenocarcinomas of the gastro-oesophageal junction, there was modest attenuation (not shown). After reclassifying participants according to BMI and their smoking history, we found risks of adenocarcinomas of the oesophagus increased monotonically with BMI among never smokers. There was no evidence that combined exposure to obesity and heavy smoking led to higher or lower risks than predicted under an additive model ( $S = 0.6$ , 95% CI 0.3 to 1.4). Generally similar patterns were observed for adenocarcinomas of the gastro-oesophageal junction.

### DISCUSSION

We found consistently higher risks of adenocarcinomas of the oesophagus and gastro-oesophageal junction among obese people than among those in the healthy weight range. Our data suggest that the risks associated with obesity are independent of the risks associated with symptoms of gastro-oesophageal reflux and other factors. Indeed, these epidemiological data might be cautiously interpreted as evidence for synergistic activity between high body mass and gastro-oesophageal reflux in promoting adenocarcinomas of the oesophagus, and to a lesser extent, the gastro-oesophageal junction.

Obesity has previously been shown to be a determinant of gastro-oesophageal reflux in many studies,<sup>9–11 13 14</sup> although not

all.<sup>28</sup> Obesity has also been associated with Barrett's oesophagus<sup>29</sup> and oesophageal adenocarcinoma.<sup>16–20</sup> A pathway through which the effect of obesity is mediated by gastro-oesophageal reflux would be a parsimonious explanation for the observed association between obesity and oesophageal adenocarcinoma.<sup>15</sup> Our finding that risks of adenocarcinoma were only modestly attenuated after including the effects of gastro-oesophageal reflux argues against this simple model, however. Moreover, we and others<sup>16–19</sup> have found obesity to be associated with significantly increased risks of oesophageal adenocarcinoma even among people who had never experienced symptoms of reflux. Because the risks of combined exposure to high BMI and frequent symptoms of gastro-oesophageal reflux were significantly higher than the sum of the independent risks, we speculate that obesity plays a further part in the development of oesophageal adenocarcinoma, over and above its likely role in promoting reflux. Earlier analyses have suggested higher risks of BMI in the presence of reflux, although neither of those studies formally assessed biological interactions.<sup>18–30</sup>

Smoking significantly increased the risk of oesophageal and junctional adenocarcinomas, but there was no evidence of an interaction with body mass. Among never smokers and those with a modest smoking history, risks of both cancers were significantly higher among obese than non-obese people. However, among heavy smokers, there was no difference in risk of oesophageal adenocarcinoma between healthy, overweight or obese people. Qualitatively similar observations with stronger effects of BMI among never smokers have been made previously.<sup>18</sup> This pattern of association might be partly explained by the effects of smoking on lowering body mass.<sup>31–32</sup>

Our study had strengths and weaknesses. The large samples of patients newly diagnosed with oesophageal and gastro-oesophageal cancer were prospectively identified and ascertained from the Australian population, and were compared with a large control series sampled from a population register. Neither participants nor interviewers were informed of the study hypotheses, minimising the possibility of biased recall. Objective measures of adiposity (such as the waist–hip ratio or waist circumference) are generally preferred to self-reports of weight and height for studies investigating causal associations.<sup>14</sup> Such measures are not appropriate for case–control studies where cancer is the end point, however, because case participants in such studies have typically lost considerable amounts of body mass in the period preceding their diagnosis, and often also as a consequence of treatment.

Similarly, we had no reliable measures of past infection with *Helicobacter pylori*, which has been negatively associated with gastro-oesophageal reflux and oesophageal adenocarcinoma<sup>33</sup> and has been implicated in suppressing appetite and body weight<sup>34</sup> and thus might potentially confound the association between BMI and oesophageal adenocarcinoma. We did ask participants whether they had ever been clinically diagnosed with this infection, noting that this would require a blood or breath test, or endoscopy. In our sample, the self-reported prevalence of clinical diagnosis for *H pylori* infection was 6.3% among controls, 6.8% among oesophageal adenocarcinoma cases and 8.5% among gastro-oesophageal adenocarcinoma cases, considerably lower than the prevalence estimates of 30–40% reported in recent population-based serological studies of asymptomatic Australian adults.<sup>35–36</sup> Adjustment for this self-reported measure made no difference to the risk estimates, and was not included in the final models.

Although we cannot entirely exclude recall bias as a source of error, several observations argue against differential reporting of

BMI as an explanation for our findings. First, risk estimates for each measure of BMI were consistently higher for adenocarcinomas of the oesophagus than the gastro-oesophageal junction, a specific pattern of risk unlikely to be due to biased recall by study participants. Second, the overall association was specific for adenocarcinomas but not SCCs (data not shown). This suggests that the effect of BMI is not simply due to over-reporting of body mass by all patients with “oesophageal cancer”.

Our participation rates were less than ideal, leading to concerns about selection bias. The age and sex distribution of the participating cases was similar to the distribution of all potentially eligible cases notified to the Australian national cancer statistics clearing house (2002); however, further details of non-participating cases were not available from registries owing to privacy laws. Risk estimates would be biased upwards if the prevalence of the key exposures of interest (namely obesity and gastro-oesophageal reflux) was lower among our control group than the target population. We dealt with this problem by comparing the BMI distribution in our control series with those reported by the Australian National Health Survey (NHS) conducted in 2004, a representative survey of the Australian adult population. BMI was similarly distributed among our controls and NHS participants. Moreover, we compared our study BMI risk estimates with those derived using models that imputed the NHS BMI distributions onto our control series (manuscript under review). Risk estimates for the effect of BMI were essentially unchanged by this procedure, suggesting no appreciable bias due to a selected control sample.

The prevalence of at least weekly symptoms of reflux among our population sample of controls (12% among men and 11% among women) was similar to prevalence estimates from other population surveys in Australia,<sup>37</sup> the UK<sup>9</sup> and Sweden.<sup>38</sup> We therefore consider the likelihood of biased selection on the basis of this symptom to be no greater than for previous studies.

Assuming our findings reflect true causal associations, the question arises as to how obesity might cause oesophageal adenocarcinoma. Increased reflux frequency remains one plausible mechanism, since high BMI and anthropometric measures of obesity have been associated with frequent reflux symptoms,<sup>8–9–12–14–39</sup> as well as with asymptomatic acid reflux and erosive oesophagitis.<sup>40–41</sup> Central adiposity is postulated to promote acid reflux, possibly through increased intra-abdominal pressure,<sup>42</sup> although data in support of a mechanical effect of obesity are weak.<sup>43</sup> Other mechanisms through which obesity might induce reflux have also been advanced.<sup>44</sup> Arguing against the notion that obesity increases the risk of oesophageal adenocarcinoma simply by inducing reflux was our finding that the risk estimates associated with BMI were only modestly attenuated by including measures of symptomatic reflux in regression models. Moreover, we found that obesity remained a highly significant risk factor even among people with no reported history of reflux.

Might other factors have a role? Recent interest has focused on the endocrine effects of adipose tissue and its potential role in carcinogenesis. With obesity, there is generally an increase in insulin production, which in turn leads to the synthesis of insulin-like growth factor (IGF-I). Both these hormones can stimulate cell proliferation and inhibit apoptosis—conditions which are conducive to cancer development and for which there is some evidence of an effect.<sup>45</sup>

Fat cells also produce peptide hormones such as leptin, adiponectin and resistin, collectively known as adipocytokines, some of which have been shown to have mitogenic and

angiogenic effects in a variety of tissues including the oesophagus.<sup>46,47</sup> The role of leptin warrants further scrutiny, as its expression is upregulated in wounds<sup>48</sup> and it has been shown to promote repair of gastric ulcers<sup>49</sup> and skin wound when applied systemically and topically.<sup>50</sup> One might speculate that the higher levels of leptin among the obese may promote proliferation of oesophageal epithelial cells, particularly when inflamed. Whether adipocytokines enhance proliferation in oesophageal tissues in the absence of inflammation is not known, although such a mechanism would explain our finding of higher risks of oesophageal adenocarcinoma cancer among obese people without symptoms of reflux. An alternative explanation is that obese people have higher rates of asymptomatic reflux and oesophagitis, and that this phenomenon underlies the observed association.

In summary, these data confirm that obesity independently increases the risk of adenocarcinomas of the oesophagus, and to a lesser extent, the gastro-oesophageal junction. From a clinical perspective, these data raise the prospect that patients with obesity and frequent symptomatic reflux are at especially increased risk of adenocarcinoma. Understanding the mechanisms through which these exposures might cause cancer is the focus of our continuing research.

**Acknowledgements:** We thank Harish Babu MD for his assistance with pathology abstractions. This study was supported by the Queensland Cancer Fund and the National Health and Medical Research Council (NHMRC) of Australia (Program No 199600). David Whiteman and Penelope Webb are supported by senior research fellowships from the National Health and Medical Research Council of Australia and Queensland Cancer Fund, respectively. Shahram Sadeghi and Nirmala Pandeya are supported by PhD scholarships from the Ministry of Health and Medical Education of IR Iran and the National Health and Medical Research Council of Australia, respectively. The funding bodies played no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or preparation, review or approval of the manuscript.

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**Competing interests:** None.

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## Editor's quiz : GI snapshot

Robin Spiller, editor

### Obstructive jaundice following a myocardial infarct

#### Clinical presentation

A 70-year-old man presented with a non-ST elevation myocardial infarction. Physical examination, ECG and blood tests including liver function tests were normal. Treatment with aspirin, clopidrogel and enoxaparin was commenced.

The chest pain resolved. However, from the third day there was an obstructive pattern in his liver function tests without abdominal symptoms (bilirubin 238 mmol/l, alkaline phosphatase 480 IU/ml, aspartame transaminase 156 IU/ml). This derangement coincided with a decrease in haemoglobin by 3 g/l. Given a recent diagnosis of prostatic carcinoma, a differential diagnosis of pancreatic head mass, possibly of metastatic or primary malignant aetiology, causing obstructive jaundice was made on initial imaging.

Multi-slice computed tomography (CT) illustrated calcification within the pancreatic head, consistent with chronic pancreatitis and a 6.5 cm mass was demonstrated within the pancreatic head intimately related to the gastroduodenal artery, with similar enhancement to that in the aorta (fig 1).

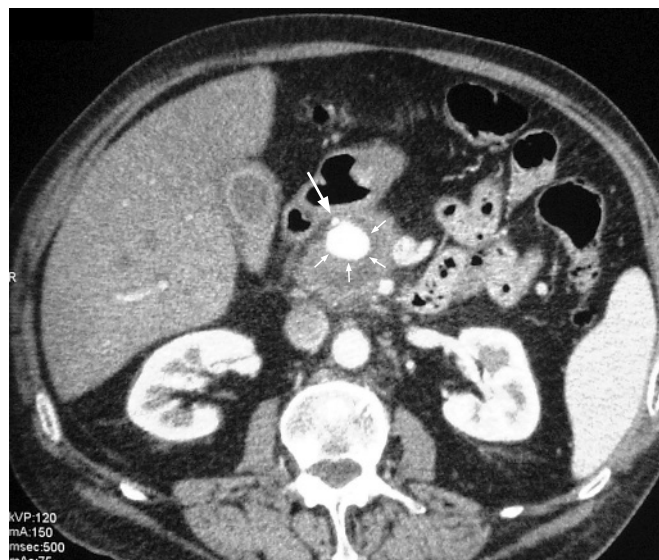
#### Question

What is your diagnosis and how would you manage this condition?

See page 187 for answer.

**J N Khan,<sup>1</sup> R Sanyal,<sup>2</sup> A Pallan,<sup>1</sup> J Ferrando,<sup>1</sup> J Ment,<sup>1</sup> S Roy-Choudhury<sup>1</sup>**

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**Figure 1** Contrast enhanced multi-slice abdominal CT scan showing the gastroduodenal artery (large arrow), with the 6.5 cm intimately related enhancing mass (small arrows).

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**Competing interests:** None.

*Gut* 2008;**57**:180. doi:10.1136/gut.2006.103804