Obesity and the rising incidence of oesophageal and gastric adenocarcinoma: what is the link?

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While data support an association between BMI and oesophageal adenocarcinoma, it is not known why the cancer incidence differs so markedly by gender and ethnicity

The incidence of oesophageal adenocarcinoma has increased over 500% in some countries during the last three decades, but the reasons for this rise are unclear.¹ The most intractable problem to date has been explaining why the rates for oesophageal adenocarcinoma vary substantially by race (more common in Caucasians), gender (more common in men), and geography.¹⁻⁶ The increasing prevalence of obesity in society may provide a partial explanation for the increases in incidence. The article by Merry *et al.* in this issue of *Gut* describes a well-designed cohort study which evaluates whether measures of body size, such as height and the body mass index (BMI), are associated with the subsequent risk of oesophageal and gastric cardia adenocarcinomas (see page 1503).⁷ Its strengths include its cohort design, high-quality data, the ability to evaluate BMI early in adult life (when carcinogenic processes such as Barrett's oesophagus may begin) and with weight gain, the completeness of cancer follow-up, the large size (which permitted stratification by gender), and its evaluation of different cancer types within a single population. The study adds knowledge particularly in two areas. First, it found that a high baseline adult BMI and increases in BMI after the age of 20, but not BMI at age 20, were strongly associated with oesophageal adenocarcinoma and cardia adenocarcinoma; this suggests that interventions aimed at preventing weight gain in adulthood may decrease the risk of oesophageal and cardia adenocarcinomas. Second, it provided detailed evaluations of height, which demonstrate no clear association between height and oesophageal or cardia adenocarcinomas. This finding suggests it is excess body weight for any given height, rather than a peculiarity of the BMI ratio equation, that accounts for the associations between BMI and these malignancies.

Is the study by Merry *et al.*⁷ consistent with the existing literature on the associations between BMI and oesophageal

adenocarcinoma? Yes. Several publications indicate that there is an association between increasing BMI and the risk of oesophageal adenocarcinoma, although the magnitude is moderate. Recent systematic reviews of the association between BMI and the risk of oesophageal adenocarcinoma identified 14 studies that evaluated the relationships between body fat and oesophageal or cardia adenocarcinomas (two cohorts and 12 case-control studies, totalling 2488 persons with oesophageal adenocarcinoma and 2509 persons with cardia adenocarcinomas). A high BMI (>25) was associated with an increased risk of oesophageal adenocarcinoma in both men and women (men OR = 2.2; 95% CI, 1.7 to 2.7; women OR = 2.0; 95% CI, 1.4 to 2.9) and higher BMIs were associated with a higher cancer risk (overweight men OR = 1.8; 95% CI, 1.5 to 2.2 vs obese men OR = 2.4; 95% CI, 1.9 to 3.2).⁸⁻⁹ Thus, the current study is concordant with prior data, but it still raises the question of how BMI might increase cancer risk.

A potential causal pathway from body size to cancer may be from normal to gastro-oesophageal reflux disease (GORD) to Barrett's oesophagus to oesophageal adenocarcinoma and some gastro-oesophageal junction adenocarcinomas. People with Barrett's oesophagus, a metaplastic change of the oesophagus, have a 30-40-fold increased risk of oesophageal adenocarcinoma.¹⁰ In such a direct pathway, cancer risk factors, such as BMI, could act by increasing the prevalence of GORD, by increasing the prevalence of Barrett's oesophagus among people with GORD, or by enhancing the risk of malignant transformation from Barrett's oesophagus to adenocarcinoma. Other factors (eg, smoking, diet or genetics) may also influence the steps on this pathway; for example, environmental exposures such as smoking may influence whether someone with GORD develops Barrett's oesophagus, or whether someone with Barrett's oesophagus develops cancer. However, if the main pathway starts with GORD, then decreasing the risk

of reflux alone might be expected to proportionately decrease the risk of the subsequent steps in the pathway: Barrett's oesophagus and oesophageal adenocarcinoma. Therefore, knowledge of when putative risk factors act is crucial for timing potential interventions.

The first question then becomes, might BMI increase the risk of cancer simply by increasing the chance of gastro-oesophageal reflux disease? Two recent statistical syntheses of the associations between BMI and GORD found moderate positive associations between increasing BMI and GORD in the USA, but not consistently in other countries, and some high-quality studies showed no association.⁸⁻¹¹ Thus, there may be a general, though not strong, relationship between BMI and GORD symptoms. The main barrier to this line of reasoning for the carcinogenic pathway is that GORD symptoms do not track strongly with cancer risk in the population as a whole. GORD is common among men and women, and in all ethnicities, but the risk of cancer is markedly higher in Caucasian men.²⁻¹²

The second question might be whether BMI increases the risk of Barrett's oesophagus, independent of GORD. In other words, among two persons with equivalent amounts of GORD, will the heavier person be more likely to develop Barrett's oesophagus?¹³ Several large case-control studies that may partially address this question are under way and results from the first studies suggest that BMI alone is not a strong risk factor for Barrett's oesophagus.¹⁴

Finally, might BMI increase the risk of Barrett's oesophagus progressing to adenocarcinoma of the oesophagus or gastro-oesophageal junction, independent of GORD? Although BMI and abdominal size may be risk factors for the malignant progression of Barrett's oesophagus, it is unclear from the existing small studies whether this is independent of GORD.¹⁵⁻¹⁶ A substantial barrier to research on reflux is the imperfect association between GORD symptoms and acid reflux. Persons with severe acid reflux may have few symptoms and, conversely, some with severe symptoms may have modest reflux. If this affected all groups equally, we might make some comparisons, but there are data to suggest this may not be the case. A study of employees at a US veterans hospital suggested that, for similar symptoms, African-Americans were less likely to have oesophagitis.¹⁷ It may also be that only an isolated oesophagitis from a brief vomiting illness or a toxic injury (rather than prolonged periods of reflux) is sufficient to create Barrett's oesophagus. In short, little is known regarding why only some people with GORD develop Barrett's oesophagus and the risk factors for progression

from Barrett's oesophagus to oesophageal adenocarcinoma.

Cumulatively, the data extant suggest that gastro-oesophageal reflux is common but that, even at similar levels of BMI, waist size or reflux symptoms, individual characteristics may influence the risk of oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma among patients with GORD. Three published studies have evaluated one such individual characteristic, abdominal obesity, in selected populations. A study of 36 veterans with Barrett's oesophagus who had undergone an abdominal CT scan for any reason versus controls suggested that increased abdominal fat was a risk factor for Barrett's oesophagus independent of BMI.¹⁸ Another study of patients with Barrett's oesophagus suggested that the risk of histological, flow cytometric and genetic abnormalities rose with increasing abdominal fat but not with increasing BMI,¹⁶ implying that the fat distribution pattern may be more influential than the absolute BMI as a risk factor for oesophageal adenocarcinoma. A third community-based study found that waist circumference, independent of BMI (and not BMI itself), was a risk factor for Barrett's oesophagus.¹⁴

Can there be GORD-independent pathways for oesophageal adenocarcinoma? Though minimal data exist, this seems plausible. BMI and obesity have been associated with several types of cancers that are unrelated to GORD, and the fat distribution pattern may influence general cancer risk to a greater degree than overall adiposity.^{9 19 20} Even though abdominal obesity may increase the risk of GORD through mechanical mechanisms, via increased intra-abdominal pressure, this association is unproven and there are minimal population-based data on the associations between abdominal size and reflux symptoms.^{12 21} Abdominal obesity (separate from general obesity) has also been found to increase the risk of many cancers, including cancers of the breast and colon,^{22 23} even though none of these cancers is associated with GORD. Abdominal obesity is also more common among men, making this a potential explanation for the demographic patterns of oesophageal adenocarcinoma. It is thus feasible that BMI and oesophageal adenocarcinoma may be linked through GORD-independent mechanisms or that these mechanisms may modify the individual response to GORD and GORD-induced mucosal damage, but do any pathways make biological sense?

There is a body of evidence that suggests that body fat is metabolically active and it may mediate cancer risk, in part, by altering levels of intermediary hormones that modulate inflammation, healing and cell

growth.^{22 24-26} Adipose-associated polypeptides such as leptin, adiponectin, insulin-like growth factors and ghrelin represent potential GORD-independent mechanisms for the mediation of cancer risk, or they may mediate the individual response to GORD or even GORD itself. These peptides can modulate mucosal inflammation and healing, have associations with cancer risk for other malignancies, and have plausible biological mechanisms for modifying cancer risk at the cellular level through the modulation of cell proliferation, apoptosis (cell death), angiogenesis (new blood vessel formation) and the cell cycle.²⁷⁻³⁰ The adipokines may also vary by gender, possibly by ethnicity and by distributions of body fat (eg, abdominal versus peripheral body fat). These compounds may thus be in the pathway between obesity and oesophageal adenocarcinoma, may partially explain this cancer's unusual gender and ethnic distributions, and represent an interesting area for future inquiry.

In summary, the existing data on oesophageal adenocarcinoma raise as many questions as they do answers. The study by Merry *et al.* provides additional prospective data supporting an association between BMI and oesophageal adenocarcinoma, but the minimal data on whether this association is mediated solely through acid reflux and the discordance between the prevalence of GORD symptoms and cancer risk by sex and ethnicity leave open the main question: why does the cancer incidence differ so markedly by gender and ethnicity? The answer to this question may direct promising avenues for cancer prevention.

Gut 2007;**56**:1493-1494.

doi: 10.1136/gut.2007.124255

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Competing interests: None.

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