

Case Study

Obesity and oesophageal adenocarcinoma: underlying mechanismsNatalie Fairhurst¹ and Richard Owen²¹*Medical Sciences Division, University of Oxford, UK*²*Nuffield Department of Surgical Sciences, University of Oxford, UK*

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Key Learning Points**Richard Owen**

Oesophageal adenocarcinoma is the most common type of oesophageal cancer in Western countries. Unfortunately, oesophageal cancer is often diagnosed too late for curative treatment due to vague or non-existent early disease symptoms limiting early detection. More advanced oesophageal cancers may present with dysphagia by which time the cancer has often already spread into the lymphatic system, exacerbated by the absence of an oesophageal serosal barrier. This results in a very poor overall 5 year survival in oesophageal cancer of 15%.

The incidence of oesophageal adenocarcinoma increased markedly in the later part of the 20th century, in contrast to the decreasing incidences of oesophageal squamous cell cancer and gastric adenocarcinoma. The main risk factor for oesophageal adenocarcinoma is Barrett's oesophagus, a change from squamous to columnar epithelium in the lower oesophagus, which increases the risk of developing oesophageal adenocarcinoma 30-60 times. Barrett's oesophagus occurs in response to lower oesophageal inflammation, such as caused by gastro-oesophageal reflux disease. Obesity is a risk factor for gastro-oesophageal reflux disease as the prolonged increased intra-abdominal pressure can overcome the natural anti-reflux mechanisms. Consequently, obesity has been proposed as a cause of the increasing oesophageal adenocarcinoma incidence though more direct effects of fat containing diets on carcinogenesis have also been implicated.

Once diagnosed with oesophageal adenocarcinoma, less than a third of patients will be suitable for curative treatment by resective surgery, and thus most patients will undergo medical treatment or radiotherapy mostly aimed at improving quality of life and life expectancy. Surgery for oesophageal cancer has a significant impact on quality of life. Since postoperative recurrence of oesophageal adenocarcinoma is not uncommon accurate disease staging is critically important to avoid unnecessarily reducing patients' quality of life. Once oesophageal adenocarcinoma is diagnosed by oesophagoscopy and biopsy, patients undergo assessment of the local and distant spread of oesophageal cancer with CT and PET-CT. Patients may also undergo endoscopic ultrasound for further local and nodal staging information and diagnostic laparoscopy to check for peritoneal spread of cancer. Aside from disease staging, patients also need assessment for fitness to undergo such major surgery, often with an objective technique such as cardiopulmonary exercise testing.

Before surgery, most patients with oesophageal adenocarcinoma will undergo neoadjuvant treatment with either chemotherapy or chemoradiotherapy, as both have been shown to improve survival and reduce cancer recurrence risk. Malnutrition is a common side effect of oesophagectomy and neoadjuvant therapy, meaning that establishing a reliable non oral enteral feeding route is an important consideration. Jejunostomy is the preferred enteral route as this avoids parts of the stomach that may be required to reconstruct the upper gastrointestinal continuity after oesophagectomy. Jejunostomy is typically performed at the same time as oesophagectomy, or before as a separate procedure in patients at higher malnutrition risk, such as those with dysphagia undergoing neoadjuvant therapy. The role for chemotherapy and radiotherapy after oesophagectomy is less established, with postoperative treatments generally reserved for special cases of incomplete resection or advanced nodal disease.

Introduction

The incidence of oesophageal adenocarcinoma (OA) in the Western World has drastically increased by almost 400% in the last 30 years, making it the 8th most common cancer in the World¹. This cancer normally presents in late-stage disease meaning that therapeutic options are limited, and contributing to a five-year survival rate of only 15%². Given this, identification of modifiable predisposing factors is crucial in order that therapeutic intervention can be targeted correctly.

Across the Western World, obesity is emerging as a risk factor for various cancers³. But the evidence in support of obesity as a risk factor for oesophageal adenocarcinoma is limited and even conflicting.

Case Report

Ms CW is a 59-year-old woman who works part time as a lunchtime supervisor in a primary school, living at home with her husband. She presented to her GP with a 2-month history of progressive dysphagia. In addition she recalls a 7kg weight loss but no other accompanying symptoms.

Oesophago-gastroduodenoscopy (OGD) revealed thickening and ulceration of the distal oesophagus with a segment of epithelial dysplasia, suggestive of Barrett's oesophagus. Biopsy revealed a well-differentiated adenocarcinoma of the oesophagus with Barrett's metaplasia, Her-2 1+negative. As is routine in such cases, a PET-CT was conducted in order to stage the disease. This showed a 35mm FDG avid mass in the distal oesophagus as well as a benign adrenal adenoma but no nodal disease or distant metastases. Staging laparoscopy showed no peritoneal disease, and supported the use of surgical intervention. CW underwent 3 cycles of neo-adjuvant chemotherapy in order to shrink the tumour prior to surgery. A repeat PET-CT revealed an ill-defined distal oesophageal focus reduced to 19mm and (of potential importance as discussed below) a small hiatus hernia with reactive physiological FDG uptake in the bone marrow. CW was therefore a suitable candidate for oesophagectomy.

Ms CW had a previous tonsillectomy in youth, a laparoscopic cholecystectomy (2005), suffers obstructive sleep apnoea (for which she does not tolerate CPAP) and suffered a sternal fracture in a previous RTC. CW's current medical issues include Type 2 Diabetes Mellitus, hypothyroidism, depression, anaemia, hypertension and

she has a BMI of 49.4. She is allergic to penicillin and takes a number of regular medications (Table 1).

With regards to risk factors for adenocarcinoma, CW does not smoke and rarely drinks alcohol.

CW underwent a left thoracoabdominal oesophagectomy together with insertion of a feeding jejunostomy. Given the significance of the surgery, a bed was prepared in ICU for post-op management. Notwithstanding, CW's oesophagectomy was performed without intraoperative complications. CW experienced few post-operative complications, including chest infection and a bilious leak from the feeding jejunostomy but this was not deemed to be significant. CW was discharged home with post-op follow-up in clinic.

Discussion

The prevalence of obesity in developed countries has risen significantly in the last twenty years bringing with it an increase in obesity-associated morbidities such as cardiovascular disease and Type II Diabetes. However, a lesser-explored relationship is that between obesity and cancer. Epidemiological studies have partly attributed this association to the metabolic and endocrine effects of adipose tissue, estimating that 15-20% of all cancer deaths can be attributed to obesity⁴. The incidence of oesophageal adenocarcinoma in particular experienced a 6-fold increase in the United States from 1975-2001, a trend which is consistent across several other countries⁵. In contrast, the incidence of oesophageal squamous cell carcinoma has remained constant.

The mortality rates for oesophageal adenocarcinoma are high, with five-year survival rates standing at 15%². The poor outcome of the disease is in part because most cases present in late-stage disease where effective treatment is limited. It has therefore been suggested that identifying potential modifiable risk factors may aid early therapeutic intervention. Risk factors for oesophageal adenocarcinoma are poorly described in the literature. Incidence has been shown to be affected by race and sex: OA is four times more common in whites than in African-Americans and there is a seven-fold greater risk in men⁶. However, although the incidence among young females is quantitatively lower, it appears the rate of development is increasing at an equivalent rate. The cause for this sudden disproportionate increase is unknown. Epidemiological studies have also shown a significant geographical influence thus it is likely that environmental factors also play a role in disease development⁷.

The only known modifiable risk factor for the development of oesophageal adenocarcinoma is its precursor disease Barrett's oesophagus, a chronic inflammatory condition in which the normal squamous epithelium is replaced with metaplastic columnar epithelium. Identifying modifiable predisposing factors that lead to this disease will aid in early prevention.

Various groups have hypothesised that obesity may be an underlying factor contributing to the development of many cancers, including oesophageal adenocarcinoma. These studies and systematic reviews have evaluated the link between raised BMI and risk of developing oesophageal adenocarcinoma, concluding that there is a strong association between these two conditions^{1,7,8}. A study by Merry et al. also assessed the influence of height on development of oesophageal adenocarcinoma in order to eliminate any effect that height may have on BMI. The study concluded that there was no association between height and incidence of OA, supporting the idea that excess

Medication	Dose
Cetirizine	10mg/ OD
Folic Acid	5mg/ OD
Gliclazide	80mg/ OD
Levothyroxine	75mg/ OD
Lisinopril	2.5mg/ OD
Metformin	1g/ OD
Pioglitazone	30mg/ OD
Sertraline	100mg/ OD
Loperamide	2mg/ PRN

Table 1

body weight alone may be a contributing factor to the development of oesophageal adenocarcinoma⁹.

The mechanism by which obesity predisposes to oesophageal adenocarcinoma is unclear. Three main proposals frequently appear in the literature: 1) An increased intra-abdominal pressure caused by a large habitus increases the risk of gastro-oesophageal reflux disease (GORD), leading to Barrett's oesophagus and malignant progression to adenocarcinoma 2) Dietary factors such as a low intake of fruits and vegetables and high intake of red meat and fat may predispose to malignancy 3) A GORD-independent pathway, such as fat distribution pattern and hormonal effects of adiposity may influence a general increased cancer risk

The first proposed mechanism suggests that the fairly well established causal progression from gastro-oesophageal reflux disease (GORD) to Barrett's oesophagus to oesophageal adenocarcinoma may be attributable to an increased body size⁷. It is known that people suffering from Barrett's oesophagus have a 30-fold increased risk of developing oesophageal adenocarcinoma and that 1 in 10 people with GORD will develop Barrett's oesophagus¹⁰. Various factors have been proposed to contribute to GORD including hiatal hernias, increased gastrin production (such as in Zollinger-Ellison syndrome), medications and increased BMI. The biological mechanisms responsible for the link between obesity and GORD are thought to be an increased intra-abdominal pressure, lengthier gastric emptying, decreased lower oesophageal sphincter pressure and increased transient sphincter relaxations which all lead to extended exposure of the oesophageal epithelium to gastric acid¹¹. In addition, vagal abnormalities which occur in obesity may lead to a greater production of bile and pancreatic enzymes which are irritant to the oesophageal epithelium¹². However, this link between GORD and oesophageal adenocarcinoma has been scarcely assessed because very little valid data are available owing to the difficulty in measuring and classifying reflux. Furthermore an analysis by Lagergren identified that the increase in obesity and the increase in oesophageal adenocarcinoma incidence differ substantially, as well as the discrepancy between male and female risk¹⁵. Despite this, the likely causal relationship between obesity and oesophageal adenocarcinoma cannot be overlooked. Instead, additional carcinogenic mechanisms must be contributing.

A number of studies have also attributed diet as both a predisposing and protective factor¹⁴⁻¹⁶. Literature review suggests that vitamin C, fruits and vegetables, carbohydrates, fibre and iron are all linked to a reduced incidence of oesophageal adenocarcinoma whereas an increased calorie and fat intake may increase risk¹⁷. However, this area lacks sufficient primary data on which to base robust conclusions.

A third mechanism involved in the interplay between obesity and OA development may be the metabolic activity of adipose tissue. Theories propose that the Western lifestyle may increase cancer risk through changes in insulin and insulin-like growth factor (IGF) metabolism^{15,18}. The anabolic signals released by both insulin and IGF-I are thought to promote tumour development by inhibiting cell apoptosis and encouraging proliferation. Evidence already links these factors to the development of colorectal, breast and pancreatic cancer¹⁹. Furthermore, chronic hyperinsulinaemia, a condition which occurs in the obese population and those suffering from type 2 Diabetes Mellitus has been linked to increased cancer development.

The obese population are not only more likely to suffer metabolic disturbances linked to insulin resistance but are also exposed to a greater concentration of circulating oestrogens and androgens which are synthesised by the adipose tissue itself. If oestrogen were a potential protective mechanism then this would suggest that with increased obesity and thus increased volume of oestrogen-producing adipose tissue, the incidence of oesophageal adenocarcinoma would decrease as BMI increases. Given this is not the case, the mechanism of hormonal imbalance needs further research.

One factor that may account for the discrepancy between male and female risk of developing OA is the distribution of adipose tissue. Men have more abdominal obesity than women which may further increase their risk of oesophageal adenocarcinoma. Abdominal obesity has been linked to cancers of the breast and colon, offering a plausible GORD-independent mechanism for the development of oesophageal adenocarcinoma²⁰. Experimental evidence suggests that greater abdominal visceral obesity enhances aberrant insulin signalling and increased concentration of endogenous oestrogen and androgen which can lead to carcinogenesis, as is the case in breast cancer. Conversely, the disparity between incidence in male and female oesophageal adenocarcinoma suggests oestrogen may instead be protective.

Alternative evidence suggests that adipose-associated peptides may also mediate carcinogenesis. Peptides such as leptin, adiponectin and IGF can alter mucosal inflammation and healing by modulating cell proliferation, angiogenesis and apoptosis, ultimately leading to tumour growth^{7,21}. Differing types and ratios of adipokines may in part elucidate the unexplained gender and ethnicity distributions and warrant further investigation.

Public Health England report that 63.8% of adults in England are clinically 'overweight' with £6.1 billion of the NHS budget being spent on obesity-related healthcare every year.²² Public awareness of this modifiable risk factor should not only encourage health checks but should motivate people to attempt weight loss.

Attempts to increase public awareness of the link between obesity and cancer development have recently experienced a boost in the form of the Cancer Research UK campaign, identifying that obesity is the second biggest preventable cause of cancer after smoking. However, the public response to the campaign, reprimanding the charity for 'fat-shaming' and for encouraging body dysmorphia²³, suggests that the population do not (or do not want to) recognise the health risks obesity entails.

Although obesity and GORD are risk factors for oesophageal adenocarcinoma, it is evident that other modifiable risks also contribute to disease development. Ms CW did not complain of reflux disease suggesting that her obesity alone (via GORD-independent mechanisms) was the major contributor to her cancer development, with Type II Diabetes Mellitus likely adding to disease burden.

Although there is evidence to support all of the above three mechanisms, none of these factors currently explains the predominance of disease in men and white westerners. Considering that oesophageal adenocarcinoma typically presents in late-stage disease, demonstrates poor morbidity and mortality and has few curative treatment options, further clinical investigation is required in order to identify specific predisposing factors which can be targeted therapeutically to mitigate against disease development and progression.

Conflicts of interest

None.

Funding

None.

Consent

The patient has consented to the publication of this case study.

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