



## Cancer of the oesophagus – *quo vadis?*

Oesophageal carcinoma is the seventh leading cause of cancer death worldwide. It is a devastating disease with very few patients 'cured' once diagnosed. The disease has two contrasting pathological (and epidemiological) forms. Squamous carcinoma of the oesophagus (SCO) is primarily a disease of the underprivileged, with an association with poverty and malnutrition and a higher incidence in developing countries. It comprises over 90% of cases diagnosed worldwide. Adenocarcinoma of the oesophagus (ADO), though equally devastating, is primarily a disease of the privileged, with a high association with obesity and a 'Western' diet. It is one of the few malignancies that have shown an increase in incidence over the past two decades.

In general, malignant tumours arise either from external factors (such as carcinogens, radiation, and viruses) or internal factors (such as hormones, immune conditions, and inherited mutations). Causal factors may act together or in sequence to initiate or promote carcinogenesis. It is estimated that up to 75% of all malignancy may be preventable through lifestyle modification such as cessation of smoking, avoidance of alcohol, weight control and other 'habitual' modifications. The time between carcinogen exposure or mutations and the development of detectable malignancy is often 10 years or more, so preventive measures need to be early and sustained. Carcinoma of the oesophagus is distinguished as the malignancy with the highest regional variation. This has led to optimism that epidemiologists may be able to identify preventable or treatable causes. Alternatively, the identification of high-risk groups will allow early case detection and more effective treatment.

The highest rates of incidence of SCO are in the Linxian region of northern China and the Caspian Sea littoral in Iran, Turkey and Kazakastan. Closely following this are regions in the Eastern Cape of South Africa (the former Transkei). In the Caspian littoral sharp gradients in incidence occur, where within 500 km the incidence decreases by a factor of 70 as one moves westward. Locally, in the Eastern Cape there are similar differences as one travels from east to west, with the incidence in the Centane and Butterworth districts notably higher than in the Lusikisiki and Bizana districts. Within areas of high incidence there is often 'case clustering' such as described by Burrell around illegal shebeens, implicating the peculiar brewing techniques, ingredients and containers used.<sup>1</sup> Factors such as these give credence to the causal nature of SCO.

### Identified epidemiological factors

**Alcohol and tobacco.** The American Cancer Society estimates the age-standardised relative risk of SCO in smokers to be over 7 times that of non-smokers for males and over 10 times

for females. In most areas of Europe the incidence of SCO is low. In Brittany (a province in Western France) the incidence is over twice that of the rest of Europe. This parallels the high incidence of death from cirrhosis and other alcohol-related disease. Neither smoking nor drinking alone have nearly the same effect as when the two are used in synergy.<sup>2</sup> Ethanol is not considered a carcinogen, but may act as a co-factor by helping carcinogens that exist in tobacco smoke to diffuse across the mucosal barrier. Other forms of tobacco use such as snuff and the chewing of pipe residua (*isixaxa*) are highly mutagenic but not so common. However, this does not account for high incidence of SCO in some predominantly Muslim areas where alcohol use is infrequent.<sup>3</sup> In addition, the rising incidence of ACO over the past 2 decades does not parallel changes in the use of tobacco or alcohol or in the incidence of tobacco-related malignancies.

**Socio-economic status and diet.** SCO tends to occur in areas of low income where vitamin deficiency is common and diets often are dependent on monocereal staples. Frequently there are coexistent diseases such as pellagra, rickets and tuberculosis. Conversely, ACO tends to occur in more affluent countries and there is a high association with obesity, a low intake of dietary fibre and high intake of saturated fats.

**Age, race and sex.** Rates of SCO are highest in the 7th and 8th decades except in endemic areas where median ages are often the 5th and 6th decades. ACO is notable for its reputation of striking in middle age. SCO has a race and sex predilection for black males. American black males have a rate of occurrence of SCO 2 - 10 times greater than that for white males living in the same region. SCO accounts for over 80% of oesophageal malignancy in black males, with ADO comprising over 50% of cases in white males. In 1995, ACO overtook SCO as the leading cause of oesophageal cancer in Western white males. In all races, males have a higher incidence than females for both ACO and SCO, ranging from 20:1 in France to 2:1 in local series.

**Pre-existing disorders.** A number of conditions are associated with a higher than normal incidence of SCO: (i) Plummer Vinson/Patterson Kelly syndrome (oesophageal web formation, iron deficiency and glossitis); (ii) achalsia; (iii) oesophageal diverticulae; and (iv) caustic oesophageal injury.

For ACO the following are considered risk factors: (i) Barrett's oesophagus; and (ii) oesophageal reflux.

**Genetic predisposition.** Tylosis (keratosis palmaris et plantaris) is an autosomal dominant disorder characterised by abnormal hardening of the palms and soles and papillomas of the oesophagus. It carries a 90% risk of SCO by age 70. It occurs in small family groupings primarily in Europe and America. The abnormal gene is on chromosome 17q25. Though



familial clustering occurs, it can often be explained by socio-economic and habitual similarities.<sup>4</sup>

**Infectious agents.** An association between human papillomavirus (HPV) and SCO has been drawn in studies from Asia.<sup>5</sup> This does not seem to be a factor in Western studies. *Helicobacter pylori* has been associated with gastric carcinoma in endemic areas such as Columbia, China and Finland. Recent series have shown a reverse association with ACO.<sup>6,7</sup>

**Geographical factors.** Local cases of SCO have been noted to follow geological strata. In these areas, soils have been found to be deficient in iron, copper, zinc and particularly molybdenum. The latter is integral in plant enzymes causing increases in nitrates. The remainder are essential for the breakdown of nitrosamines to ammonia and amino acids. In general high soil concentrations parallel higher incidences of SCO.

**Mucosal irritation.** In an article in this issue of *SAMJ* Matsha *et al.*<sup>8</sup> observe an association between self-induced vomiting and the presence of chronic oesophageal inflammation. Their observations appear to have identified a significant 'cofactor' in the development of SCO. Numerous studies have also noted the presence of chronic oesophagitis which parallels the incidence of SCO, particularly in endemic zones.<sup>3,9</sup> In addition, chronic reflux (and inflammation) has been causally implicated in ACO. It remains controversial whether there is a direct association between gastro-oesophageal reflux disease (GORD) and ACO. Symptomatic reflux has been found to be a significant risk factor for oesophageal adenocarcinoma.<sup>10,11</sup>

### Can intervention influence incidence?

A pivotal question is that if this (or any other malignancy) is truly preventable, can any interventional strategy reduce incidence or mortality? For SCO there is a suggestion of the protective effect of vitamin supplementation in high-risk individuals.<sup>12</sup> Improved nutritional standards including increased consumption of fresh fruit and vegetables may be protective.<sup>13</sup> A study of an endemic 'hotspot' in Iran observed a markedly reduced incidence of dysplasia which paralleled the improvement in diet and socio-economic indicators. In a parallel area where the socio-economic standard had not

improved the rate of SCO remained very high.<sup>14</sup> A recent study suggests that drinking and smoking cessation programmes can reduce the risk of oesophageal malignancy.<sup>15</sup> Whether anti-reflux surgery can alter the incidence of ACO remains unproven.<sup>16</sup> Epidemiological data provide relative support for non-steroidal anti-inflammatory agents, particularly aspirin, in chemoprevention of oesophageal carcinoma.<sup>17</sup>

Locally, there appears to have been a reduction in SCO cases over the past decade. Whether this reflects a true reduction in case incidence or a change in referral patterns remains to be determined. What is also evident is that there is currently a remarkable increase in ACO. Could this be paradoxical payback for the economic upturn in recent years?

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