



Alastair M Sammon

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# **SQUAMOUS CANCER OF THE OESOPHAGUS IN AFRICA**

Alastair M Sammon

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## Introduction

Oesophageal cancer is the sixth most common malignancy worldwide. More than 80% of oesophageal cancers are in poor countries. The disease there is almost all squamous carcinoma, a different disease in terms not only of geographical distribution but also of aetiology, site, and presentation from adenocarcinoma – the predominant form in richer countries. In most countries of the world including some in Africa the incidence of oesophageal cancer is in low single figures per 100,000 people per year; in other parts of Africa it may be as much as a hundred times more. In Transkei, with the highest ever reported incidences in Africa, the disease is described as ‘endemic’.

There is no common agreement about the aetiology of Squamous Cancer of the Oesophagus (SCO) in Africa. Until there is agreement, then action will not be taken to reduce the incidence of this disease which besets many communities in Africa, is nearly always incurable, and kills in a slow and particularly miserable way.

My hope in launching this book and the associated forum is to stimulate debate on the causes of Squamous Cancer of the Oesophagus, to focus attention on gaps in our knowledge; to encourage a multidisciplinary, logical and comprehensive approach to aetiology and through that to make prevention possible.

The book is intended to be a resource for researchers, a catalyst for ideas for research into the aetiology of ESCO and an attempt to interpret all the data available and make sense of it.

By restricting illustrations to a minimum the book and website have been kept to a size that can be reasonably downloaded by those with slow internet access.

The first version of this book inevitably reflects my own viewpoint. I look forward to receiving and publishing competent challenges and additions – the essence of a forum.

Alastair Sammon  
Gloucester, England 2009

# Summary

## Chapter summaries

1 **History** Oesophageal cancer was rare in East, Central and Southern Africa until the 1930s. Its incidence has risen rapidly since then to make it one of the commonest cancers in the region, and in some areas the leading cause of death.

2 **Squamous cancer in non-endemic areas** Tobacco and alcohol are the two constant associations with SCO worldwide in low and medium incidence areas. Each has a linear, dose-related effect. Using both alcohol and tobacco has a synergistic effect.

Specific predisposing conditions in low and medium incidence countries have in common a reduction in oesophageal exposure to acid; some also involve reflux.

3 **Disease description** Cancer of the oesophagus in Africa presents usually with dysphagia for fluids, weight loss and dehydration. 97% is squamous. It occurs predominantly in the middle third of the oesophagus. Both late presentation and limited medical facilities dictate that treatment is normally palliative and survival normally brief.

4 **Incidence** In most countries of the world the annual incidence rate of oesophageal cancer is less than 10 per 100,000 people. Males predominate. Three areas of the world have very high incidences: Linxian province in China, The Caspian Littoral region, and Transkei in South Africa. The highest reported incidence is 547.2 per 100,000 males aged 35-64 in Kazakhstan on the Caspian Littoral. Throughout East, Central and Southern Africa there is a high incidence. Unlike other high incidence areas of the world, Africa's high incidence has arisen in the last century, from a negligible start. Dramatic differences in incidence exist over short distances.

5 **Who gets SCO?** In Africa, the most susceptible population is rural, involved in subsistence farming of poor land. Their chief crop and chief food is maize. They are poor but with some education and some cash income. There is no ethnic pattern. In rural Transkei, an endemic area, there is a marked abnormality of upper gastrointestinal function including gastric acid suppression, heartburn, and reflux.

6 **Case-Control Studies** Case-control studies all confirm that the most susceptible group is rural or has a rural base, and is transitional in terms of culture and education; the group is of low education and socio-economic status. There is a strong association with tobacco usage, but not with alcohol in close case-controlled studies in endemic areas. The most susceptible population has a traditional diet of maize, pumpkin and beans. There is a strong and dose-related association with use of maize meal. A high-level association with *Solanum nigrum* was found in one study.

7 **Environmental studies** The environment indirectly affects foods of subsistence farmers. There is no proven direct association between environment and SCO.

8 **Foods I – Maize** Maize has a consistent and genuine association with SCO, but its history in Africa is much longer than that of SCO. It has steadily taken over from other staples throughout much of East, Central and Southern Africa. Maize meal is the form of maize most strongly linked to SCO, has the greatest deficiencies and the greatest degenerative chemical change; there is a dose-related effect and a high relative risk. In the middle of the twentieth century, the sudden rise in oesophageal cancer was paralleled by a rise in the use of maize, a change to white dent maize, and easy availability of commercially milled maize to rural people.

9 **Maize, linoleic acid and prostaglandin E2** A maize-based, otherwise poor diet has a very high omega-6 to omega-3 fatty acid ratio, and because of this increases PGE2 production throughout the body, including the gastric mucosa. Linoleic acid in esterified form mediates a slow sustained production of PGE2. Nonesterified linoleic acid causes a rapid and temporary increase of PGE2 production in the gastric mucosa.

There are significant effects of intragastric PGE2 on upper GI function including acid suppression and upper GI reflux. These same effects are produced by maize consumption; the slow effects by a maize-based diet, the rapid effects by maize meal. PGE2 is also directly mitogenic to the oesophageal mucosa.

10 **Foods II – other foods** Alcohol is not a risk factor in endemic areas for SCO. Vitamins and mineral supplements have usually been given in multiples. The one micronutrient that passes the tests of proven deficiency in endemic areas - significant lower levels in SCO victims, and significant improvement on supplement is deficiency of selenium. Lower level evidence exists against deficiencies of riboflavin, vitamin E and beta-carotene.

*Solanum nigrum* and lima beans have evidence of a positive association with SCO from a single case-control trial only, but both have the possibility of being major aetiological factors since they have highly significant associations. Pumpkin also has scanty evidence against it except as part of the Transkei diet of maize, pumpkin and beans, but a significant association may be present.

The protective value of dietary fat is strongly supported by two case-control studies in very high risk areas.

Fresh fruit and vegetables have evidence of a protective effect worldwide, but inconsistent evidence in high-risk areas.

11 **Carcinogens** No single potent carcinogen has been found on which the endemic incidence of SCO can be blamed. There is good evidence that no such undiscovered potent carcinogen exists. Tobacco is an important carcinogen in Africa with a dose and time-related effect. In the absence of tobacco there would still be a very high incidence of SCO in endemic areas. Human papillomavirus is associated in a minority of cancers, and this may be a causal association. Nitrosamines are found in the environment but not at such a level that they could explain the very high incidences found. Plant mycotoxins are present in the environment and the evidence would support a minor role in the carcinogenic process: fumonisin B1 is not a proven carcinogen for the human oesophagus in the amounts so far demonstrated in Africa. The pattern of genetic damage in endemic areas is different from those in areas where the disease is more sporadic.

12 **Reflux** Duodenal fluid reflux into the oesophagus is carcinogenic. Duodenal reflux without gastric content is significantly more powerfully carcinogenic. The evidence supports gastric acid as being a protective factor. In humans, conditions which are associated with reflux and acid suppression including pernicious anaemia, gastrectomy and alcohol consumption, are also associated with squamous carcinoma.

13 **What causes oesophageal cancer?** High level and consistent evidence exists to associate SCO with maize as the monostaple, the diet of maize pumpkin and beans, maize meal consumption, tobacco, and low dietary fat intake. Lower level but consistent evidence supports a link with human papillomavirus, and deficiencies of vitamin and selenium intake. Pumpkin, beans and *Solanum nigrum* have high-level but inadequately corroborated evidence implicating them. Other agents including fumonisins, nitrosamines, traditional beer and alcohol have had adequate research and have no convincing evidence against them.

The evidence points to diet as the base for endemic incidences of the disease. A high maize meal intake, poverty of dietary fat and dietary deficiencies including selenium are the best evidenced associations.

The history of the availability of commercially milled maize and the time-scale of the 'epidemic' are compatible with a causal association.

14 **A proposed aetiology of ESCO** Maize meal, a low-fat diet, and other microdeficiencies including selenium, together create an excess production of PGE2 in the stomach. Excess PGE2 causes inhibition of gastric acid production, and duodeno-gastro-oesophageal reflux. These physiological abnormalities are carcinogenic.

Each of these steps is evidenced in theory. Each step has good corroborating evidence in high-risk and endemic areas of Africa.

This aetiological chain provides an explanation for the high incidence of the disease in certain areas, its timescale, apparent spread, the lack of influence of alcohol in endemic areas, and the targeting of the rural transitional population.

Other factors which boost the incidence of SCO in certain communities and individuals include tobacco, HPV, pumpkin and beans, and may also include *Solanum nigrum*.

15 **Preventative actions** On the basis of already broadly accepted ideas of causation, health education to ensure a variety of diet, and education about the very high danger of tobacco in the endemic situation are all justified, but not likely to be immediately or highly successful. The most logical education message is that added dietary fat is preventative.

Stabilisation treatment of maize meal and strict distribution and storage conditions may be both effective and achievable. Omega-3 fatty acid supplementation of maize meal, if possible in cost and taste terms, is an alternative which would at the same time make a good contribution to general health.

For the generations already long-exposed to the endemic base factors, strict avoidance of carcinogens may be the only preventative option.



# 1 History

## Chapter Summary

Oesophageal cancer was rare in East, Central and Southern Africa until the 1930s. Its incidence has risen rapidly since then to make it one of the commonest cancers in the region, and in some areas the leading cause of death.

## Chapter Content

### A low start

### Rising incidence

### An epidemic

### Confounding issues

### Discussion

### Conclusion

#### A low start

There is evidence that the incidence of cancer of the oesophagus was low in all of Africa up to 1930:

Cook (1971) reports a negligible incidence in 1930-1940. Cancer of the oesophagus was rare in South Africa in 1930s (Berman 1935). Burrell (1962) reports that the disease was unheard of among the Xhosa people of Transkei until the late 1930s, and in some areas later than that. There is no mention of cancer of the oesophagus in cancer surveys of Zululand, Natal and Transvaal before 1920 (Rose 1979). Cancer of the oesophagus represented less than 1% of all malignancies diagnosed between 1913 and 1923 at Lovedale Mission Hospital, South Africa (Macvicar, 1925). Strachan (1934) writes of the results of 3851 postmortem examinations in Johannesburg in 1934, when only 3 oesophageal cancers were found in black men.

#### Rising Incidence

Van Rensburg (1981) stated that in central and Southern Africa, within four decades esophageal cancer emerged from a virtually unknown disease to attain almost epidemic proportions.

A rising incidence has been reported in many African countries over several decades after 1930:

Kenya (Cook and Burkitt 1975; Ahmed 1966)

within four decades oesophageal cancer emerged from a virtually unknown disease to attain almost epidemic proportions
---

Western Kenya and Uganda in the 1950s and 1960s (Cook 1971)  
Uganda (Wabinga et al 2000)  
Rhodesia (Gelfand 1971)  
Swaziland (Keen and Martin 1971)  
Botswana (Macrae and Cook 1975)  
Urban blacks in South Africa (Bradshaw and Harington 1987).

The rise in incidence has been most remarkable in South Africa. Hospital records for Transkei and Ciskei show a slowly increasing incidence from 1930 onwards, with an explosive rise after 1940. Rose (1979) plots the rising incidence of CO in Transkei, showing a more than 600% rise in the years 1950 to 1965. This rise applies principally to the black population. Cook (1971) calculates a 5.3-fold increase in this diagnosis in Johannesburg between the early 1950s and early 1960s. Higginson and Oettle (1960) reported that by 1954 it was the commonest tumour in African males at 10.3% of all cancers. In 1964 the corresponding rate was 27.5%. Coetzee (1966) reported a sixfold increase in hospital admissions to Edenvale Hospital in Natal between 1953 and 1964. Burrell (1957) also reported a rising incidence. The rise in incidence from about 1950 was also confirmed by changes in the ratio of oesophageal cancer compared to cancers of other sites (Bradshaw et al 1983). Cook (1971) calculated an incidence rate of 246.2 per 100,000 for men aged 35-64 in Transkei. Doll (1969), using data from Rose (1967) calculated the rate as 357.2 per 100,000 persons aged 35-64.

From 1968-77 SCO was the commonest cause of death in urban South African blacks. The disease also has a high incidence in coloured (mixed race) people, but is low in the white and Asian communities (Bradshaw and Harington 1987). A significant rise was noted in the presentations of SCO to Baragwanath Hospital, Johannesburg between 1950-54 and 1960-64 (Warwick and Harington 1973).

## An epidemic

The epidemic character of oesophageal cancer in Transkei was first described in 1955 (Warwick and Harington 1973). Bradshaw et al (1983) also wrote of 'a sustained and relentless epidemic of apparently recent onset which at present shows no signs of abating'. Rose (1979) wrote of an 'explosive rise'.

a sustained and relentless epidemic of apparently recent onset

The concept of oesophageal cancer as an epidemic was further fuelled by some researchers who perceived a pattern of geographical spread from an epicentre in Transkei (Oettle et al 1986; Keen 1977a). Certainly the rise in incidence in Transkei started early and proceeded to record the highest incidence figures for Africa. However other high incidence areas of Africa are discontinuous with the area of spread in South Africa, for instance the West of Kenya where the incidence rose sharply in the early 1960s.

## Confounding Issues

Burrell (1957) reports that post-mortem examination was taboo for Africans in the Transkei/Ciskei border area of South Africa in the 1950s with the only definitive method of diagnosis an oesophageal biopsy, which was rarely possible in those days. There is the possibility that the disease was already present, but understood to be an 'African' disease, not amenable to cure by western medicine, and therefore not presented at hospitals.

Failure to diagnose may represent lack of awareness by doctors rather than absence of the disease. Burrell (1957) gathered data on oesophageal cancer in 1952 to 1955, and reported a sudden increase in 1956 because 'our hospital interns... are more alert to an earlier diagnosis of the condition'. Wakhisi et al (2005) writing about the high incidence of the disease in Western Kenya suggest that 'the presence of experts or a particular relevant facility in an area is responsible for creating an 'epidemic''.

## **Discussion**

The positive evidence of a sudden and major rise in incidence is very strong. Strachan's presentation of the post-mortem finding of a low incidence in the earlier part of the 20<sup>th</sup> century firmly supports other evidence of a pre-existing negligible incidence in Southern Africa.

Heightened awareness, and increased reporting could have made the rise of the epidemic appear more acute. However there was already awareness of the disease in the 1930s, and serious monitoring of the incidence had already begun before the 1950s when the greatest increases occurred. The evidence is of a sharply rising incidence throughout East and Southern Africa which was independently observed in several regions.

## **Conclusion**

There has been a well documented and rapid rise in incidence of SCO in East and Southern Africa from a low level in the 1930s to among the world's highest incidences by the 1960s.

## **2 Squamous cancer in non-endemic areas**

### **Chapter summary**

Tobacco and alcohol are the two constant associations with SCO worldwide in low and medium incidence areas. Each has a linear dose-related effect. Using both alcohol and tobacco has a synergistic effect.

Specific predisposing conditions in low and medium incidence countries have in common a reduction in oesophageal exposure to acid; some also involve reflux.

### **Chapter content**

#### **Risk factors**

**Alcohol**

**Tobacco**

**Tobacco and alcohol synergism**

**Other risk factors**

#### **Specific predisposing conditions and associations**

**Corrosive cicatrisation**

**Pernicious anaemia**

**Gastrectomy**

**Achalasia**

#### **Discussion**

#### **Conclusion**

#### **Risk Factors**

##### **Alcohol**

There is a well-established association of SCO with alcohol (Schoenberg et al 1971; Mosbech and Videbaek 1955; Wynder and Stellman 1977; Tuyns 1983; Rossi et al 1982). Nearly all papers show a relative risk (RR) of at least 5.

Alcohol carries with it a greater risk for squamous cancer than for adenocarcinoma (Vaughan et al 1995; Gao et al 1994; Hashibe et al 2007; Vioque et al 2008).

There is evidence of a linear relationship with dose (Pottern et al 1981; Tuyns 1983; Wynder and Stellman 1977; Yu et al 1988; Tavani et al 1994). Lee et al (2005) demonstrated a relative risk of 13.9 for those consuming over 900g per day-year of alcohol.

Yu et al (1988) showed a highly significant trend with average daily dose of alcohol in USA.

Stopping drinking alcohol has a 10 year delay in risk reduction unless accompanied by stopping smoking (Castellsaque et al 2000).

It is not clear whether the type of alcoholic drink used is relevant: Barra et al (1990) found an Odds Ratio (OR) of 15:10:6 for wine: wine and spirits: wine spirits and beer. However Gronbaek et al's results (1988) led them to state that a moderate intake of wine probably does not increase the risk of upper digestive tract cancer, whereas a moderate intake of beer or spirits increases the risk considerably.

### **Tobacco**

There is an established strong (Schoenberg et al 1971; Tuyns 1983; Yu et al 1988) association with smoking, the risk increasing as tobacco use rises (Yu et al 1988; Wynder and Stellman 1977), and as tar content rises (La Vecchia et al 1986). The relative risk for smokers is, in nearly all papers, somewhere between 3 and 5. Snuff carries a relative risk of 1.7 (Wynder and Stellman 1977).

The association with tobacco consumption is also proven in areas of moderate risk for oesophageal cancer such as Lower Normandy, France (Jacob et al 1993) and in Northern Italy (Rossi et al 1982; La Vecchia et al 1986; Negri et al 1992).

### **Tobacco and alcohol synergism**

Alcohol and tobacco are the major risk factors in the low- and medium-risk areas of the world. They have an independent effect; alcohol is strongly associated with oesophageal cancer in non-smokers, and smoking is strongly associated with oesophageal cancer in non-drinkers (Tavani et al 1996; Tuyns 1983).

The relative risk is greater with alcohol than with tobacco. Pottern et al (1981) found in USA a RR of 1.9 for tobacco use, 6.4 for alcohol consumption. Tuyns (1983) found in France a RR of up to 5.16 for non-drinking smokers, and up to 11.04 for non-smoking drinkers.

alcohol and tobacco are the major risk factors in the low- and medium-risk areas of the world
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Lee et al (2005) detected a multiplicative effect in Taiwan for those who smoked and drank, as did De Stefani et al (1990) in Uruguay, Fan et al (2008) in Shanghai, Sakata et al (2005) in Japan, and Hashibe et al (2007) in Central Europe.

Wynder and Stellman (1977) also report a synergistic/multiplicative effect with smoking and alcohol consumption.

### **Other reported risk factors**

In France, consumption of butter is associated with CO (Jacob et al 1993).

Chewing of betel is associated in Taiwan (Lee et al 2005).

Maize meal and alcohol are associated with SCO in Northern Italy (Rossi et al 1982; Franceschi et al 1990). Rossi et al (1982) reported a RR of 6.17 for a high daily intake of maize meal. Franceschi et al (1990) reported a RR for CO of 2.8 for high maize meal consumption. This is a traditional maize growing and consuming area. It is the cereal most widely grown and is eaten in the form of polenta (maize meal).

Eskimos who constantly chew alkali during curing of skins have a high incidence of squamous carcinoma (Hurst 1964).

Consumption of *mate*, a bush tea, has a strong association with oesophageal cancer in Uruguay (Sewram et al 2003).

### **Specific predisposing conditions**

There are several known specific predisposing conditions:

#### **Corrosive cicatrisation**

Following a corrosive burn, there is an elevated risk of cancer, which is situated usually above the scar. Post-corrosive malignancies are always squamous. They occur 15 to 75 years post-burn (Sapozhnikova 1976).

#### **Pernicious anaemia**

There is an elevated risk of SCO in people with pernicious anaemia (Hsing et al 1993). The relative risk is 3.2 after 20 years. Pernicious anaemia may be associated with reduced lower oesophageal sphincter pressure (Orlando and Bozyski 1973; Castell et al 1973).

B12 deficiency is not the risk factor for SCO but pernicious anaemia is (Ye et al 2003). There is no elevated risk of adenocarcinoma.

#### **Gastrectomy**

The risk of squamous carcinoma increases within 20 years of gastrectomy, and rises with time (Maeta et al 1986; Caygill et al 1987; La Vecchia et al 1994; Tachibana et al 1995; Shearman et al 1970).

Gastrectomy is accompanied by a high rate of duodenogastric reflux (Sears et al 1995). Sears found that 10 of 13 partial gastrectomy patients had abnormal duodenogastric reflux.

gastrectomy decreases the lower oesophageal sphincter pressure, and there is a high incidence of gastro-oesophageal regurgitation

Gastrectomy decreases the lower oesophageal sphincter pressure, and there is a high incidence of gastro-oesophageal regurgitation (Iida et al

1994; Broll et al 1993). 70% of post-gastrectomy patients have symptomatic reflux (Broll et al 1993).

#### **Achalasia**

Achalasia is a major risk factor for SCO (Ellis 1960). The disease is predominantly middle third, and in Ellis's series occurred 8 to 33 years after diagnosis of achalasia. There was a 33-fold increase in risk of CO in Meijssen et al's series (1992), with an incidence of 3.4 per 1000 patients per year - equivalent to 340 per 100,000.

### **Discussion**

Alcohol and tobacco are the two major aetiological agents in low- and medium-incidence areas of the world. Tobacco is assumed to work directly as a carcinogen or as a grouping of carcinogens. The mechanism of alcohol causation is not established, nor is the reason for the synergistic combination of alcohol and tobacco.

Common threads in predisposing conditions include a lack of acid in the oesophagus (post-gastrectomy, pernicious anaemia, high alcohol intake, achalasia, stricture, alkali consumption) and reflux (post-gastrectomy, pernicious anaemia, alcohol).

## **Conclusion**

The principal risk factors for SCO are tobacco and alcohol. Achlorhydria and reflux are recurring themes in predisposing conditions.

## **3 Disease description**

### **Chapter summary**

Cancer of the oesophagus in Africa presents usually with dysphagia for fluids, weight loss and dehydration. 97% is squamous. It occurs predominantly in the middle third. Both late presentation and limited medical facilities dictate that treatment is normally palliative, and survival normally brief.

### **Chapter content**

#### **Site**

#### **Age**

#### **Presentation**

#### **Histology**

#### **Prognosis**

#### **Discussion**

#### **Conclusion**

#### **Site**

Burrell (1962) reported on over 1000 patients with oesophageal cancer in South Africa. The cancers were predominantly sited in the mid-oesophagus. Radiologically they showed stenoses of 1½ to 4 inches.

250 oesophageal cancer patients in Transkei (Cotton and Sammon 1989) had a peak incidence at 30cm, with more tumours occurring above this level than below.

#### **Age**

There is an occasional presentation before the age of 30, rising incidence with age. Mannell and Murray (1989) found the peak presentation age to be 56.

#### **Presentation**

Burrell (1957) reports from East London on the presenting symptoms of 59 patients: retrosternal pain 21, chronic unproductive cough 16, difficulty swallowing 8, vomiting 6, haematemesis 4, regurgitation 4.

Cotton and Sammon (1989) working in Transkei found much later presentations of the disease. In their patients, dysphagia was almost universal, with good localisation of the site of obstruction. Regurgitation occurred in 70% and cough or dyspnoea in 28%. Rarely the presentation was with retrosternal pain, vomiting or hoarse voice. Dysphagia for fluids was present in 72% with accompanying weight loss and



dehydration. Tracheal spillover was present in 39% and tracheal fistula in 6%. Vocal chord paralysis, pleural effusion and lung abscess were occasionally present. Dysphagia was the commonest presenting symptom at the Butterworth (Transkei) clinic in the 1960s (Rose and Procter 1970).

## **Histology**

97% of all oesophageal tumours in Transkei are squamous (Cotton and Sammon 1989). Burrell (1962) in East London reported all of 328 upper and mid-oesophageal tumours as squamous. There were eighteen adenocarcinomas in his series, and he excluded these, regarding them as extensions of gastric tumours.

## **Prognosis**

50% mortality rates in Johannesburg in the 1970s were quoted as occurring at 3.6 and 4.2 months for males and females respectively (Walker 1987). Mannell and Murray (1989) found that 22% of patients presenting to a number of hospitals throughout South Africa could have been considered for curative therapy, but that only a total of 17% were scheduled for curative or palliative operations, and only 7% treated by surgery and adjuvant therapy. The situation is worse in many other African countries where neither resection nor intubation can be offered; pain relief and injection of alcohol into the tumour are amongst the options.

## **Discussion**

the disease coincides with poverty, and poor medical availability
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Arguably early diagnosis and aggressive treatment are good and worthwhile. The disease coincides with poverty, and poor medical availability, and therefore with late presentation, often to a medical facility that cannot offer a full range of diagnostic and treatment options.

## **Conclusion**

Oesophageal cancer commonly presents too late for worthwhile treatment. Prevention is the only logical approach to the disease. Most resources would be appropriately used for prevention rather than for early diagnosis and treatment.

## **4 Incidence**

### **Chapter summary**

In most countries of the world the annual incidence rate of oesophageal cancer is less than 10 per 100,000 people. Males predominate. Three areas of the world have very high incidences: Linxian province in China, The Caspian Littoral region, and Transkei in South Africa. The highest reported incidence is 547.2 per 100,000 males aged 35-64 in Kazakhstan. Throughout East, Central and Southern Africa there is a high incidence. Unlike other high incidence areas of the world, Africa's high incidence has arisen in the last century, from a negligible start. Dramatic differences in incidence exist over short distances.

### **Chapter content**

#### **Incidence rates**

##### **General**

##### **Africa**

#### **Time trends**

#### **M:F ratios**

#### **Local variations**

#### **Geographical spread**

#### **Discussion**

#### **Conclusion**

#### **Incidence rates**

##### **General**

Nearly all available incidence figures are an aggregation of squamous cancer and adenocarcinoma. In the low incidence countries it is adenocarcinoma which is more common, and males are more often affected. Worldwide, however, squamous cancer predominates, with males more often affected.

In most countries of the world the incidence of oesophageal cancer is in single or low double figures per 100,000 males aged 35-64 per year: for instance USA (White population) 5.8, England 4.8, Netherlands 2.5. There are some areas of moderate occurrence including parts of France 25.5, the black population of Southern USA 20.5, and the Caribbean (Jamaica) 26.6 (Doll 1969).

The description of 'endemic' is used in several regions of the world: the Caspian Littoral region with a recorded incidence in Kazakhstan of 547.2 per 100,000 males aged 35-64; Transkei South Africa 357.2 per 100,000 persons aged 35-64 (Doll 1969); Linxian Province China - there is one report of a prevalence rate in the population over 30 years of age of 379 per 100,000 persons (The coordinating group for research on etiology of esophageal cancer in North China, 1975). In these 'endemic' regions almost all of oesophageal malignancies are squamous (Cotton and Sammon 1989; The coordinating group for research on etiology of esophageal cancer in North China 1975; Gholipour et al 2008).

in several areas of Transkei the incidence was so high that 20% of men would be affected before 75 years of age, in the absence of other causes of death

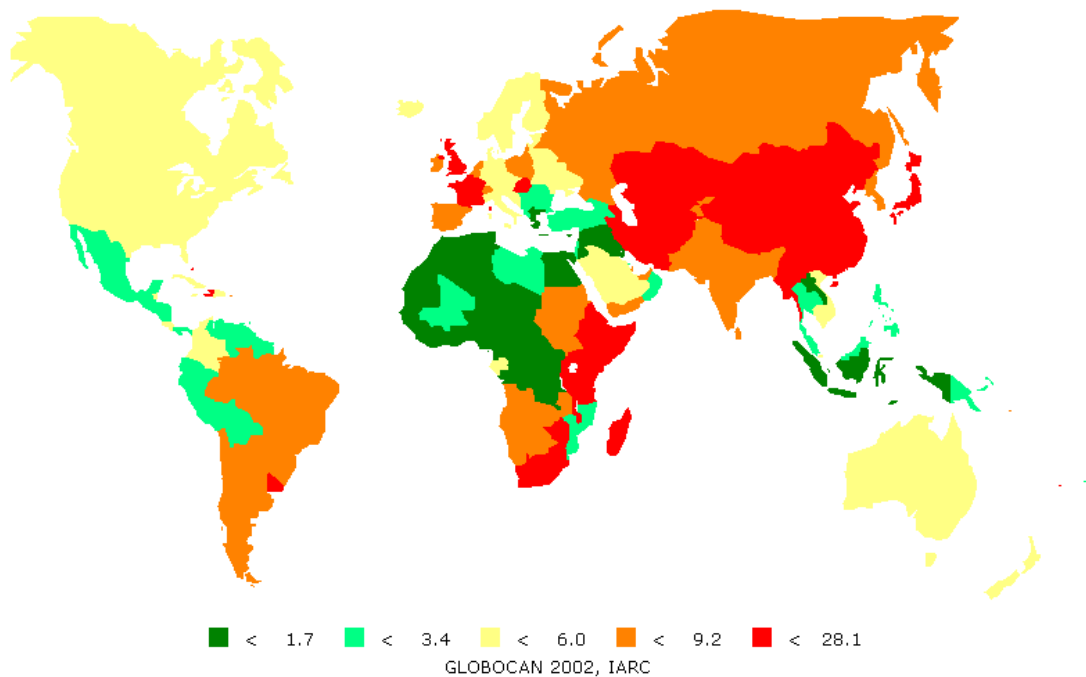
SJ van Rensburg (1979a) writes that in several areas of Transkei the

incidence was '...so high that 20% of men would be affected before 75 years of age, in the absence of other causes of death ...'. In Linxian, oesophageal cancer accounts for 20% of total deaths (Yang 1980).

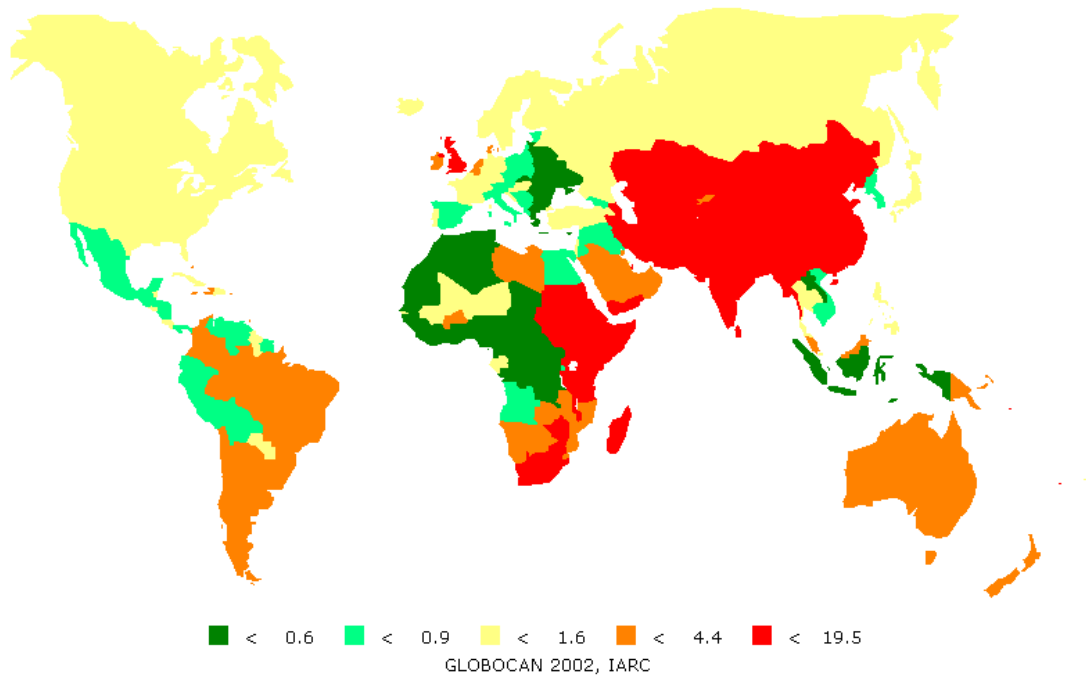
Some incidence figures for Africa are estimates, and there are some estimates for the same region that conflict.

## World

Oesophagus, Males  
Age-Standardized incidence rate per 100,000



Oesophagus, Females  
Age-Standardized incidence rate per 100,000



**World - ASR over 18/100,000 males (excluding Africa)**

China	27.4
Fiji	21.8
Kazakhstan	20.9
Mongolia	24.5
Papua New Guinea	19.4
Turkmenistan	20.7
(Globocan 2002 - Ferlay et al 2004)	

## **Africa**

### **Incidence (ASR) of cancer per 100,000 males**

#### **Over 10/100,000**

Lesotho	16.4
Malawi	16.4
Rwanda	11.5
Swaziland	13.8
Uganda	12.9

#### **Over 18/100,000**

Burundi	19.1
Comoros	19.1
Djibouti	19.1
Eritrea	19.1
Madagascar	19.1
Somalia	19.1
Tanzania, United republic of	19.9
Zimbabwe	18.1

#### **Over 20/100,000**

South Africa	20.7
Ethiopia	28.1
Kenya	22.7

(Globocan 2002 - Ferlay et al 2004)

### **Africa regional incidences**

African areas of very high incidence are:

#### **South Africa**

Transkei 357.2 per 100,000 persons aged 35-64 (Doll 1969)

Durban African population 93.1 per 100,000 persons 35-64 (Doll 1972)

#### **Zimbabwe**

Bulawayo 94.9 per 100,000 persons (Doll 1972)

157.5 per 100,000 persons aged 35-64 (Doll 1972)

58.6 per 100,000 males (Parkin et al 1994)

#### **Kenya**

Western Kenya Up to 169 per 100,000 males (Ahmed and Cook 1969).

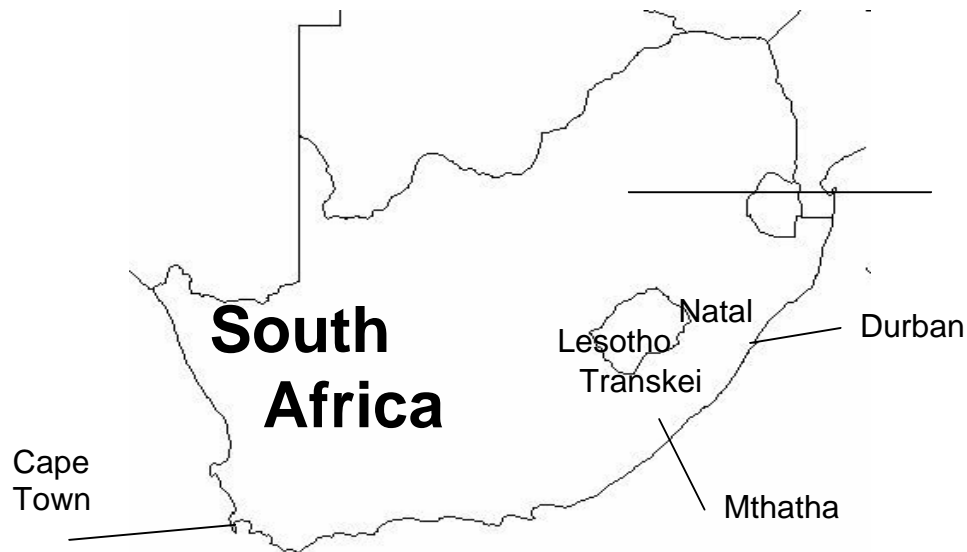
The inconsistencies relate to incomplete information being available, and also reliance sometimes on population registry of cancers and sometimes on hospital registry.

### **South Africa**

#### **ASIR per 100,000 for Black males in Southern Africa**

SA Black males overall	23.1
Johannesburg	14
Natal black males	40.9
Transkei North	22.4
Mthatha(Umtata) central Transkei	62.5
Transkei South	102.6

Incidence rates from 'Cancer in Africa' (2003 Ed. Parkin et al)



### **Transkei**

Transkei, at one stage a 'homeland' of the Xhosa people, now incorporated back into South Africa, lies on the Eastern coast. It has a coastline of 250km and an area of 16,000 square miles. It has the highest recorded incidence of SCO in Africa. Incidence rates are quoted variously and include:

357.2 per 100,000 persons aged 35-64 (Doll 1969)

246.2 per 100,000 men in the Butterworth district (high risk area) (Cook 1971, recalculating from Rose's figures)

102.6 per 100,000 males in the high risk areas (Parkin et al 2003)

76.6 per 100,000 males in Transkei (Somdyala et al 2003).

### **Time trends**

Chapter 1 (History) showed a well documented and rapid rise in incidence of SCO in East and Southern Africa from a low level in the 1930's to among the world's highest incidences by the 1960s.

For comparison, in Linxian, China, there was no significant variation in rates over the thirty years 1941-1970 (The coordination group for research on etiology of esophageal cancer in North China, 1975); there was a slight decrease in CO in China from 1973 to 1992 (Ke L 2002).

The incidence has also reduced in the Caspian Littoral by more than 50% over the last 30 years to an ASR of 134.7 for males per 100,000 (Semnani et al 2006).

During this time of increase of the disease in Transkei major social changes included a prolonged drought in the 1930s with severe loss of cattle; improvement in road works/communications; repeated monoculture of maize until maize occupied 90% of the cultivated land – 96% in high rainfall zones, with low yields, poor quality of crops. (Warwick and Harington 1973). Medically there was an awareness and search for the oesophageal cancer in the population and a continuing epidemic of tuberculosis (tuberculosis had been endemic since the turn of the century and might have disguised the concurrent epidemic of oesophageal cancer). Another significant

another significant social and dietary revolution was the introduction of small-scale rural hammer mills from about 1930

social and dietary revolution was the introduction of small-scale rural hammer mills from about 1930 onwards. Manufactured in South Africa from 1928, the first factory was in East London.

### Local variations

Variation within countries may be marked. Rose (1978) showed that oesophageal cancer rates were consistently high in Butterworth in the South of Transkei, and consistently low in Lusikisiki in the Northern part. ASR for males 1964-1969 was 102.6 per 100,000 in the high incidence area of Transkei; 59.5 in moderate risk areas, and 22.4 in low incidence areas (Parkin et al 2003). This difference became less over time (Jaskiewicz et al 1987a; Makaula et al 1995).

There is a 2.5-fold variation in incidence in different places in Zimbabwe. Parkin et al (1994) who described this difference raised the possibility of availability of medical resources to diagnose as a confounding problem. In Western Kenya 20-25% of all tumours are oesophageal, but in the neighbouring part of Tanzania 1% of all tumours are oesophageal (Rose 1977).

in Western Kenya 20-25% of all tumours are oesophageal, but in the neighbouring part of Tanzania 1% of all tumours
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Similar differences occur within Kenya where Ahmed (1966) reported incidences ranging from less than 0.4 per 100,000 people up

to 12.5 per 100,000 within a small geographical area in Western Kenya. There are major differences in incidence between Southern Malawi (high incidence) and Northern Malawi (low incidence); and between South East Zambia (high incidence) and North East Zambia (low incidence) (Cook 1971).

There may be a marked variation even from one valley to the next. Burrell et al (1966) described this in Transkei, and it was confirmed by a study (van Rensburg 1979) which showed significant spatial clustering of SCO cases. A higher incidence of SCO was found close to the home of other SCO victims. The investigators found only spatial and not time-related clustering.

### M:F Ratios

M:F ratios vary greatly. In 1954 the M:F ratio was 26:1 in Johannesburg (Higginson and Oettle 1960). The incidence for nearly all countries is significantly higher for males. In Western Europe it is 5.4:1; United States 4.6:1; Eastern Africa 2.4:1; Southern Africa 2.8:1 (Ferlay et al 2004).

In endemic areas, the ratio is generally closer. In Linxian, China the rate is 1.5:1 (Lu et al 1985). In North China the average is 1.6:1. One study found that the higher the incidence rate was the lower the corresponding M:F ratio. (The coordinating group for research on etiology of esophageal cancer in North China. 1975).

Rose (1982), and Somdyala et al (2003) both reported a M:F ratio of 2:1 in Transkei; Makaula et al (1995) a ratio of 2.4:1.

Mohebbi et al (2008) found a M:F ratio of 1.1:1 in The Caspian Littoral area of Iran.

### Geographical Spread

Keen (1977a) and Oettle et al (1986) saw a picture of 'geographical spread' in the changing incidence of oesophageal cancer in Southern Africa, to the extent of suggesting an 'epidemic' nature of spread, starting in Transkei in 1948, passing through Johannesburg in 1952, and arriving at the Rhodesian border in 1967.

## Discussion

Cook and Burkitt (1971) assert that SCO has 'the strangest distribution of any tumour in Africa'. Keen (1977a) and Oettle et al (1986) thought that there was a pattern of spread of the disease in Africa. Exact times and incidences are not all available for Africa, however the incidence of oesophageal cancer was already high in Western Kenya by the early 1960s (Ahmed 1966; Cook and Burkitt 1971) with no equivalent rise in each intervening

country. The pattern is neither consistently

SCO has the strangest distribution of any tumour in Africa

contiguous nor consistently centrifugal from one point and is more that of a steady rise in all countries in East, Central and Southern Africa since the middle of the 20<sup>th</sup> Century, with some areas suffering more than others and with much higher peaks of incidence than others.

## Conclusion

The disease varies very greatly in incidence, with significant differences between regions and within regions. There are three areas in Africa where there has been a report of a very high incidence; Transkei in South Africa, Western Kenya, and Bulawayo in Zimbabwe, all with reported incidences of over 100 per 100,000 males. Incidences increased in Africa since about 1930; in other high incidence areas of the world this did not happen.



## 5 Who gets SCO?

### Chapter summary

In Africa, the most susceptible population is rural, involved in subsistence farming of poor land. Their chief crop and chief food is maize. They are poor but with some education and some cash income. There is no ethnic pattern. In rural Transkei, an endemic area, there is a marked abnormality of upper gastrointestinal function including gastric acid suppression and heartburn and reflux.

### Chapter content

#### Socioeconomic status and education

#### Staple diet

#### Geochemical factors

#### Ethnic/genetic factors

#### The oesophageal milieu

#### Precursor lesions

#### Discussion

#### Conclusion

#### Socio-economic status and education

Communities where oesophageal cancer occurs at high incidence in Africa are poor rural communities where most are subsistence farmers. Within these, the individuals who get the disease tend to be poor but not the poorest, have a little cash income and a little education.

Bradshaw et al (1969) found that in black patients in Natal, more oesophageal cancer patients could read English, and they had more schooling than lung cancer and other

the highest risk group are those with rural assets but an ability to earn a modest income external to the subsistence economy
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cancer groups.

Van Rensburg et al (1985a), also working with Zulu patients in Natal, found that the highest risk group are those with rural assets but an ability to earn a modest income external to the subsistence economy – people in a transitional state of Westernisation. A rural mud home, ownership of agricultural land, a cash income and some education are indicators of risk. In a case-control study of 100 pairs in Transkei (Sammon 1992) 84% of patients with oesophageal cancer had 4 years or less education – people who have a little education.

Rose EF (1979) working in Transkei says the risk group is the intermediate culture - not *amaqaba* (people of the old religion and strongly traditional in their living), but *amaqoboka* (church people, who do not cling on very firmly to traditional diet or ways of preparing food) –they have nearly double the rate.

### Staple diet

Worldwide all groups of people at very high risk have a monocereal staple diet – maize (Cook 1971; van Rensburg 1987) or wheat (van Rensburg 1987). In Africa it is maize (Cook 1971; van Rensburg 1987). In Transkei the highest risk group are people who eat maize, beans and pumpkin (Sammon 1992; van Rensburg 1979b); and who eat maize meal (van Rensburg 1985a).

worldwide all groups of people at very high risk have a monocereal staple diet

### Geochemical factors

In Transkei SCO is strongly associated with sedimentary strata in the Butterworth area, with marked local variation. Locally there are lower levels of Cu, Ni, Bo, Mn, Zn, and Mb in the soil (Kibblewhite et al 1984).

Burrell et al (1966) found that Transkeians who had oesophageal cancer had gardens which were less productive, and had signs of molybdenum deficiency. Leaf changes also suggested deficiencies of iron, cooper, and zinc. Signs of malnutrition were common.

### Ethnic/genetic factors

The ‘endemic’ areas of the world - China, the Caspian Littoral region, and Transkei - are ethnically diverse. Within Africa high risk areas include ethnically diverse peoples from Ethiopia, Western Kenya, and Southern Africa.

Sheep have been afflicted with oesophageal cancer in the Cape Province of South Africa (Schutte 1968) and chickens in China (Department of pathology of CICAMS 1976). These are both high incidence areas for SCO in humans. This argues against any specific genetic problem for the humans involved and in favour of local dietary or environmental problems.

sheep were afflicted with oesophageal cancer in South Africa and chickens in China

In a study of 189 oesophageal cancer patients and 198 controls in Cape Town, Li et al (2005) found an association with the CYP2E1\*6 allele, with a relative risk of 5.9 after adjusting for age, sex, smoking and alcohol consumption. Dandara et al (2006) have identified the homozygous SULT1A1\*2/\*2 genotype in combination with CYP3A5 heterozygous genotype as having a significantly increased risk for SCO.

### The oesophageal milieu

Transkeians are a highly susceptible population. We have some evidence of what is happening in the average oesophagus in Transkei:

1 There is a bimodal distribution of intragastric gastric pH: more than half of a sample rural population of 150 people had a pH of over 4. A diet of maize (P=0.006)

and pumpkin and beans (P=0.006) was strongly associated with this absence of acid (Sammon et al 2003).

2 EGF levels in the stomach were elevated in a sample rural Transkei population of 120 people, in those who had a diet low in animal products and vegetables (Iputo et al 2004). Gastric fluid from rural Transkeians was found to be mitogenic to oesophageal cell lines (Pink 2005).

3 Heartburn and regurgitation are common in Transkei. In a sample of 50 healthy Transkeians interviewed 60% suffered from frequent heartburn, as high as the throat in 30%. It lasted from a few minutes up to 2 days, and was usually associated with eating *umqa wethanga* (a dish made from pumpkin and maize meal) or *amarewu* (a non-fermented maize meal drink) (Sammon 1994).

in Transkei:  
 high intragastric pH  
 high intragastric EGF  
 heartburn  
 regurgitation  
 self-induced vomiting  
 increased salivary PGE2

4 Many Transkeians regularly indulge in self-induced vomiting as a physical and spiritual 'purge'. In a case-control study (Sammon 1992) 91 of 100 SCO patients performed self-induced vomiting, and 85 of 100 controls. The difference in that study was not significant. Matsha et al (2006b) found 80.5% of males and 79.1% of females across all ages did this. The habit was associated with chronic oesophageal inflammation.

5 Those whose diet is very low in fat in Transkei have a markedly increased salivary PGE2 (Sammon and Morgan 2002).

Taken together these are major upper gastrointestinal abnormalities.

### Precursor Lesions

Dawsey and Wang from the National Cancer Institute in USA have carried out a prolonged prospective study of precursor lesions in an endemic area for SCO. Their first study of a cohort of 682 patients showed:

Risk of CO within 3.5 years

Normal	1
Basal cell hyperplasia	2.1
Mild dysplasia	2.2
moderate dysplasia	15.8
severe dysplasia	72.6
carcinoma in situ	62.5

(Dawsey et al 1994)

Their follow-up study of the same cohort showed:

Risk of SCO within 13.5 years

Normal	1
Oesophagitis	0.8
Basal cell hyperplasia	1.9 (0.8-4.5)
Mild dysplasia	2.9 (1.6-5.2)
Moderate dysplasia	9.8 (5.3-18.3)
Severe dysplasia	28.3 (15.3-52.3)
Carcinoma in situ	34.4(16.6-71.4)

(Wang et al 2005)

## Discussion

In Africa the poor but not poorest are at risk, suggesting a lifestyle issue -a choice

the poor but not poorest are at risk, suggesting a lifestyle issue -a choice which a little money allows

which a little money allows. The at-risk group in South Africa have maize as their staple. Within that group the at-risk sub-group are heavy consumers of maize meal. Heavy consumption of maize meal indicates being part of a cash economy, part of abandoning the traditional use of whole maize or home-ground maize only. As such it has to be seen as either another marker of the

group which is at risk; or else the maize meal is the risk itself.

The oesophageal milieu in Transkei is quite disturbed – high pH, high EGF, High salivary PGE2, and much heartburn and regurgitation associated with maize meal products. It is unlikely that these disturbances are *not* related to the incidence of SCO. Self-induced vomiting is associated with chronic oesophagitis, but oesophagitis is not a precursor lesion for oesophageal carcinoma. If

self-induced vomiting is not in fact involved in the causation of SCO, then a possibility exists that the same underlying upper gastrointestinal abnormality which causes widespread regurgitation and heartburn allows self-induced vomiting to be accomplished with more ease than in other populations.

it is unlikely that these disturbances are *not* related to the incidence of SCO

Genetic studies promise to increase our ability to identify susceptible individuals. Genetic polymorphism is unlikely to provide a complete explanation for a disease which is so geographically defined yet which crosses ethnic boundaries as thoroughly as SCO.

## Conclusion

The at-risk group is poor, but not the poorest, has rural roots but is in a transitional state of Westernisation, and relies heavily on maize meal for diet. There is no ethnic background to the disease. Genetic studies may help to identify particularly susceptible individuals. The at-risk group has a significantly disturbed oesophageal physiology.

## 6 Case-Control Studies

### Chapter Summary

Case-control studies all confirm that the most susceptible group is rural or has a rural base, and is transitional in terms of culture and education; the group is of low education and socio-economic status. There is a strong association with tobacco usage, but not with alcohol in close case-controlled studies in endemic areas. The most susceptible population has a traditional diet of maize, pumpkin and beans. There is a strong and dose-related association with use of maize meal. An association with *Solanum nigrum* was found in one study.

### Chapter content

#### Introduction

#### Segal et al

#### Pacella-Norman et al

#### Parkin et al

#### Van Rensburg et al

#### Sammon

#### Discussion

#### Conclusion

#### Introduction

There are no cohort study results available for African countries.

Case-control studies in Africa have been reported from South Africa (Segal et al, Pacella-Norman et al, Sammon, van Rensburg et al, and from Zimbabwe (Parkin et al).

#### Segal et al (1988)

In Soweto, a medium to high incidence area for SCO, 200 consecutive oesophageal cancer patients were studied and compared with 391 hospital controls. They were matched only for sex; not for age. Controls were patients with inguinal hernias, appendicitis, benign prostatic hypertrophy, cataracts and haemorrhoids. Cancer patients were excluded. There were highly significant differences in age (0.0001), salary (0.0001), possession of a car or television (0.001), and marital status (0.001). It is probable that the inclusion of appendicitis and haemorrhoids patients as controls created further selection bias towards a section of the community more removed from

traditional ways of living and eating. The patients had an average Soweto residence of 36.7 years.

A strong association with consumption of traditional beer was found (0.001). In view of the case and control selection differences this may be a genuine causal factor, or may be a marker of a different socio-economic grouping - there is insufficient evidence within the study to come to a conclusion. There was an association with tobacco consumption.

A M:F ratio of 3:1 and a possible association with alcohol consumption reflects a non-endemic situation in the population sampled. The pattern is of medium risk group - moderate education and social status, with significant involvement of alcohol and tobacco.

### **Pacella-Norman et al (2002)**

Pacella-Norman et al, in Greater Johannesburg, an area of medium to high incidence, compared 405 black South Africans with SCO and 2174 controls with cancers not associated with alcohol or tobacco. Oesophageal cancer patients were significantly less educated than controls, and had a very different age range: oesophageal cancer patients were predominantly in the 45-64 age range, their controls much more widely spread with many in the under 44 and over 65 age groups. For males tobacco had a Relative Risk of 3.8; long-term residence in Transkei had a RR of 3.1; frequent alcohol consumption had a RR of 1.8. For females tobacco had a RR of 3.1, long-term residence in Transkei a RR of 14.7, frequent alcohol consumption a RR of 1.7. Tobacco is once again confirmed as a feature as in all aetiological studies of oesophageal cancer. The clearly different educational and residential background makes it difficult to interpret the other findings.

### **Parkin DM et al (1994)**

This study is based on 826 oesophageal cancer patients whose data was available at the cancer Registry in Bulawayo, Zimbabwe, an area of very high incidence. 90%

there was no independent effect of traditional beer or of total alcohol consumption
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were SCO. 3007 controls excluded those with cancers at other sites known to be related to alcohol and tobacco. They were matched for age group, gender, education and province of origin. High tobacco

consumption had a RR of 5.6. There was no independent effect of traditional beer or of total alcohol consumption on CO.

### **Van Rensburg et al (1985a)**

211 SCO patients were studied in a Durban hospital serving mostly a mostly rural population. Patients and controls were matched for age and urban/rural background. This study provides more focus than that of Segal et al, and was carried out in an area of very high CO, short of endemic. Significantly associated factors were the daily consumption of bought maize meal (RR 5.7), cigarette smoking (RR 2.6), pipe smoking (RR 2.1), and daily consumption of butter or margarine, which was protective (RR 0.51). It is remarkable that daily buying of maize meal was significant in a culture whose staple is maize, and equally remarkable that it was very much more significant than tobacco, a carcinogen with a proven persistent association with CO. Other results show the susceptible population to be those with rural assets but an ability to earn a modest income external to the subsistence economy. There was no association with alcohol consumption.

## Sammon (1992)

This was a closely controlled study. They were almost all rural people. 100 cases and controls, matched for gender, for age in decade groups, and educational level in two-year groups. The controls were patients in the same hospital; those with undiagnosed conditions of the upper alimentary tract were excluded.

Transkei with a population of about 2 million at the time of the study (1986 to 1988) had only a very small urban population. The hospital was the referral centre for Transkei, an endemic area for CO.

This was a group of 200 rural Transkeian SCO patients and controls,

200 rural Transkeian SCO patients and controls, all of whom consumed maize, and nearly all of whom had a diet of beans and pumpkin

all of whom consumed maize, and nearly all of whom had a diet of beans and pumpkin. 80% also used wild vegetables including *Solanum nigrum*. Three quarters used traditional beer. More than half kept cows or sheep. 88% practised self-induced vomiting. 76% of cases and 53% of controls smoked tobacco. The majority of patients and controls had less than four years education. This accords with van Rensburg's

smoking  
solanum nigrum  
beans  
maize pumpkin and beans

placing of SCO victims in the category of transitional between traditional and Western ways of living.

Significant risk factors found on logistic regression analysis were: smoking, RR 2.64 (1.45-4.98), *Solanum nigrum*, RR 3.62 (1.17-5.54). Beans, used by all cases and 96 controls had a RR of 4 with undefineable

confidence interval.

A more focussed study including the original 100 cases and 100 controls was expanded to 130 case-controlled pairs (Sammon 1998a). The associations with the use of *Solanum nigrum* (RR 2.3) and smoking (RR 2.53) were confirmed. Beans (RR not calculable) and the full traditional diet of maize, pumpkin and beans were also found to be significantly associated with SCO on multiple regression analysis.

## Discussion

Segal et al's study highlighted the low socio-economic status of CO patients. Pacella-Norman et al also indicated that oesophageal cancer sufferers have low education and a rural background. van Rensburg et al's study refined that profile, showing that CO patients were predominantly people in a transitional state of Westernisation with some education and some income; purchasing more maize meal, tea, cigarettes and tobacco than controls. My own study, set in a very predominantly rural area where all people have rural assets, and controlled for educational level as well as for age and gender was further designed to eliminate the bias of socioeconomic and educational status. These studies, building on each other, therefore produced a progressively sharper focus.

The first two studies pointed out that the risk group is defined geographically, socially, and by diet. With increasing focus, there is a narrowing of factors – including the elimination of alcohol or traditional beer in endemic areas. Tobacco is a factor in all studies, but not in all people. Dietary factors were highlighted by the studies: all the

these studies, building on each other, therefore produced a progressively sharper focus

patients and controls in my study consumed maize; 96.2 % of van Rensburg's patients consumed maize meal daily; pumpkin and beans are strongly associated with SCO in my series, as is the use of *Solanum nigrum*.

It is of note that Zulus did not traditionally grow tobacco for their own use, and their urbanisation has increased the use of tobacco. In contrast Transkeians do home-grow their own tobacco.

Factors which emerge from these case-control studies as strongly associated, and potentially causally associated are:

- Consumption of commercial maize meal

- Tobacco

- Consumption of the full Transkei diet of maize, pumpkin and beans

- Consumption of *Solanum nigrum*.

## **Conclusion**

When geographic area, education/social status, gender, and age are controlled out, significant differences remain in diet and tobacco use. Consumption of maize meal, pumpkin and beans and *Solanum nigrum*, and the use of tobacco have strong statistical associations with oesophageal cancer in high risk areas of Southern Africa.



## 7 Environmental studies

### Chapter summary

The environment indirectly affects foods of subsistence farmers. There is no proven direct association between environment and SCO.

### Chapter content

#### Geochemical background

#### Cancer gardens

#### Discussion

#### Conclusion

#### Geochemical

Laker in 'Environmental Associations with Oesophageal Cancer in Transkei' (1979) took a comprehensive look at the geochemical background to the disease.

All areas of very high incidence within Transkei, the Caspian Littoral area, and Linxian, China have a low annual rainfall. In Transkei and in the Caspian Littoral area of Iran, SCO is associated with soils of low potential for rainfed cropping.

In Transkei the picture is of poor quality soil with a low mineral content. This is reflected in low nitrogen, potassium and manganese in maize leaves, and high magnesium content.

There have been observations of low levels of molybdenum and other trace elements in the soil in high risk areas of South Africa (Burrell et al 1966).

Yang (1980) reports an inverse relationship in Northern China between SCO mortality and food and drinking water content of molybdenum, manganese, zinc, magnesium, silicon, nickel, iron, bromine, iodine, chlorine, potassium, sodium, phosphorus and bicarbonate. A similar inverse relationship was found for hair content of magnesium, molybdenum and zinc.

#### 'Cancer Gardens'

The land surrounding the home of a Transkei family is normally used for growing vegetables. Burrell et al (1966) compared 'cancer gardens' i.e. gardens of homes where there was or had been a case of SCO with controls. These controls were selected apparently without being seen beforehand by the researchers, and it was reported that the cancer gardens were all obviously less productive than those which were 'tumour-free'. They reported intense molybdenum deficiency in the plants of gardens where present or previous inhabitants had had SCO, but 'less intense' molybdenum deficiency in gardens in the same area where there had been no SCO. The plants of cancer gardens were also reported to be suffering from a complex trace element deficiency. No accurate chemical sampling was carried out, and visual signs were used for the diagnosis of molybdenum deficiency. Molybdenum

supplementation of these gardens greatly improved the quality of the crops, so that molybdenum deficiency was felt to be the major factor. They mention the fact that owners of 'cancer gardens' depend more on pumpkin vine tips and edible weeds than do occupants of better gardens.

owners of 'cancer gardens' depend more on pumpkin vine tips and edible weeds than do occupants of better gardens

do occupants of better gardens. The 'cancer garden' concept was at one stage widely used in discussions on the aetiology of SCO, but the paper which first used the concept (Burrell et al 1966) can only be said to raise

the possibility rather than prove any association.

## **Discussion**

It is most likely that environmental variations, such as climate and soil are not direct causes of SCCO, but may determine the direct causes; climate and soil determine agricultural practices which influence diet, including dietary contaminants. Climate and soil also significantly affect wealth, which affects dietary and lifestyle choices.

## **Conclusion**

The soil in high risk areas is mineral-poor. There is no proven direct link between environment and SCO.

## 8 Foods I – Maize

### Chapter summary

Maize has a consistent and genuine association with SCO, but its history in Africa is much longer than that of SCO. It has steadily taken over from other staples throughout much of East, Central and Southern Africa. Maize meal is the form of maize most strongly linked to SCO, has the greatest deficiencies and the greatest degenerative chemical change; there is a dose-related effect and a high relative risk. In the middle of the twentieth century, the sudden rise in oesophageal cancer was paralleled by a rise in the use of maize, a change to white dent maize, and easy availability of commercially milled maize to rural people.

### Chapter content

#### General

#### History of maize in Africa

#### Processing of maize

#### Health effects of maize

#### Maize meal

#### The nature of the association with maize

#### Maize and SCO

#### Degeneration of stored maize meal

#### Discussion

#### Conclusion

#### General

Nearly all current thought about the aetiology of SCO includes diet or dietary contaminants. There is one undeniable association with SCO in Africa which is maize.

there is one undeniable association with SCO in Africa which is maize

A monocereal diet is the hallmark of a high-risk community. The deficiencies of maize have been blamed by van Rensburg (1981). Content has been blamed (Burrell et al 1966; Marasas et al 1988). The combination of deficiency and content has been blamed (Sammon and Alderson 1998b; Sammon and Iputo 2006).

In that maize and cancer of the oesophagus are very closely associated, one can assume that there are clues about SCO aetiology in the timescale of the introduction, changes in the production quantities and/or processing of maize.

## History of maize in Africa

Maize was first introduced to West Africa in the 16<sup>th</sup> century, into Southern Africa probably a century later, and spread northwards from the Cape. It was in common use in the nineteenth century in South Africa when sorghum was the main staple.

By 1930 maize had superseded wheat as the region's major cash crop and replaced sorghum as the major food crop. By the 1930s and 1940s black farms no longer produced food crops for the market and now relied on maize for subsistence (McCann 2005).

In the 1950s maize production in East Africa increased 66%. In Southern Rhodesia it increased fourfold.

By 1999 maize provided more than a third of South Africa's carbohydrates, a sixth of the fat, and three tenths of the protein (McCann 2005).

Maize's transition to a major crop in Kenya occurred during World War 1, when disease in millet led to famine, and millet seed was 'consumed rather than planted' (Smale and Jayne 2003). By 1960 44% of the land cultivated was maize; in the 1970s 51.4%. In 2002 maize supplied approximately half the calories of the country (McCann 2005).

Maize only became a dominant crop in Malawi well into the 20<sup>th</sup> century (Miracle 1966). Maize was a staple in Northern Rhodesia by the end of the 18<sup>th</sup> century but was no more than a minor food until the beginning of the 20<sup>th</sup> century.

within Africa the highest per capita consumption of maize is in Zambia; second is Lesotho; third is Malawi

Maize was the predominant crop in South and South West Ethiopia in 1938. It rose from 32% to 48% of national Ethiopian crop between 1986 and 1991 (McCann 2005).

Within Africa the highest per capita consumption of maize is in Zambia; second is Lesotho; third is Malawi (McCann 2005).

The first maize cultivated in Africa was flint maize. Now white dent maize has taken over and is more than 90% of Africa's crop (a much higher proportion than the rest of the world). Maize for human consumption is almost exclusively white; yellow maize is used for cattle feed and industrial purposes. This change took place in 1920s and 1930s (McCann 2005).

## Processing of Maize

Maize can be eaten as whole grain, as stamped (dehulled) maize or as various grades of milled product. The pattern of usage in rural Africa was at first use of whole grain or maize stamped, or ground for immediate use. The change to the use principally of

a major driver of change was the small hammer mill

milled maize occurred in stages in the first part of the 20<sup>th</sup> century. Machine-milled maize became available and affordable in towns earlier, but a major driver of change was the small-scale

hammer mill. These small units were factory-produced from the late 1920's (the first factory in Africa was in East London) and soon were dispersed to the trading stores of the country. Subsistence farmers could have large amounts of maize ground, take home sacks of the produce and use it over the course of weeks or months. It also became a standard food for migrant labourers. When previously they would have taken a sack of whole maize, now it would more often be a sack of maize meal; alternatively they might be provided with maize meal by their employer.

The diet in Transkei in the sixties and seventies at the height of the epidemic of CO in the highest incidence region, was very largely based on maize – whole maize, stamped maize, bought maize meal, home-ground maize meal; maize on its own, maize with beans, maize with pumpkin, maize with vegetables, maize with wild vegetables; non-alcoholic fermented maize; maize beer.

Maize was a constant daily constituent, other foods added seasonally or opportunistically. There would not always be money to buy cooking oil at the store. Meat would be eaten occasionally when there was an important occasion, and a cow, sheep or goat slaughtered in the community. Milk was a luxury which only those with cattle would have. The decline in milk consumption was coupled with an ever-increasing use of maize as a staple at the expense of sorghum, and also a low intake of meat.

Up to the 1970s sorghum was used as the malt for beer brewing in low incidence Transkei areas, maize as the malt in high incidence areas (Bradshaw et al 1983). In Mt Ayliff, Transkei in 1970 49% of people used commercial meal for beer. Samp (stamped maize) and commercial maize meal were the two main dietary components (Kirsten 1975). By this time maize had almost entirely superseded sorghum as a staple food (Rose 1982).

### **Health effects of maize**

Later in the 19<sup>th</sup> century when peasant monocropping of maize became common in South Africa, niacin was grossly deficient in the diet and pellagra became endemic for rural maize consumers (McCann 2005).

In Lesotho pellagra and kwashiorkor increased in direct proportion to the rising percentage of maize in the local diet and the decline of sorghum as a staple during the postwar years (McCann 2005).

Cook (1971) showed that the distribution of maize beer use and of SCO are similar. van Rensburg (1981) showed that the high

a significant risk of SCO for those who consumed bought maize meal daily as against those who consumed it weekly
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incidence areas of the world all have either maize or wheat as their staple. van Rensburg et al (1985a) in a case-control study in Natal, South Africa, further demonstrated a significant risk of SCO for those who consumed bought maize meal daily as against those who consumed it weekly. He regarded this as indicating more reliance on commercial maize, and therefore more exposure to deficiencies of magnesium, zinc, nicotinic acid and riboflavin.

In a high incidence area of Transkei for SCO, over 90% of meals were found to be maize-based (van Rensburg 1979b).

Maize is associated with SCO throughout Africa. This is a consistent and strong association (Cook 1971; van Rensburg 1981).

Carcinogen-driven SCO in rats was strikingly lower in rats fed millet, red sorghum, brown rice, or potatoes than when fed corn, wheat, commercial sorghum, bananas and polished rice (van Rensburg et al 1985b).

### **Maize meal**

Consumption of maize meal is associated with oesophageal cancer amongst Zulu men in South Africa (van Rensburg et al 1985a), and the people of Veneto, Italy. (P<.00001) (Rossi et al 1982). This effect is dose-related.

Maize meal is associated with an increased risk of Ca stomach (La Vecchia et al 1987) and an increased risk of cancer of oral cavity and pharynx (Franceschi et al 1991).

There is something in fresh-pounded maize oil which prevents duodenal ulceration. It is near the solvent front in the thin layer chromatography extract (Tovey et al 2005).

In Transkei it is widely accepted that certain maize-based products cause heartburn. The commonly blamed foods are *amarewu* (a fermented, non-alcoholic drink prepared from maize) and *umqa wethanga* (a stiff porridge made from maize meal and pumpkin). 60% of a sample of healthy people admitted to frequent heartburn lasting from a few minutes up to 2 days and in many cases symptoms rose as high as the

of those who suffered heartburn 73% regurgitated fluid into their mouths

throat. Of those who suffered heartburn, 73% regurgitated fluid into their mouths.

### The nature of the association of SCO with maize

Franceschi et al (1991) also showed a rising Relative Risk of oesophageal cancer with rising frequency of maize meal consumption, a RR of 2.8 for those taking 3 or more servings per week.

Van Rensburg (1985a) showed that daily against weekly consumption of maize meal carried a RR of 5.7 for SCO. There was no such association shown for homegrown maize meal, whole maize, bought or homegrown stamped maize.

Rossi et al (1982), working in Northern Italy, in a region where maize is the staple, found a linear rise with dose of maize meal: a daily consumption of over 106g had a RR of 6.17 for SCO.

While the association with maize meal is dose related, per capita maize consumption internationally does not translate into SCO rankings;

while the association with maize meal is dose related, per capita maize consumption internationally does not translate into SCO rankings

for maize consumption as percentage of national diet 2002, highest are Malawi, Zambia, and Zimbabwe, but their SCO rates are not the highest – the highest national incidences are found in Kenya, Ethiopia and South Africa. Some Latin-American countries also have a high *per capita* maize consumption but a relatively

low incidence of CO.

### Maize and SCO

Maize and/or wheat are main dietary staples in all high incidence areas (van Rensburg 1981). Maize, maize as monocrop, maize with pellagra, maize and poverty, all were prevalent in these areas long before the advent of SCO in the 1930s to 1950s.

This prompts the question as to what changes took place in early 20<sup>th</sup> century.

1 Change to white maize – also the choice of the Veneto region of Italy and Central America. The chemical difference between yellow and white maize apart from the carotene pigment of yellow maize is a small amount of vitamin A.

maize, maize as monocrop, maize with pellagra, maize and poverty, all were prevalent in these areas long before the rise of SCO in the 1930s to 1950s

- 2 Maize very widely became the monocrop.
- 3 Maize meal in large quantities became freely available in towns and in rural areas. Maize changed from a home-produced and eaten cereal to a 'marketed urban food in the form of flour, a process that began early in the 20th century' (McCann 2005).

### Degeneration of stored meal and flour

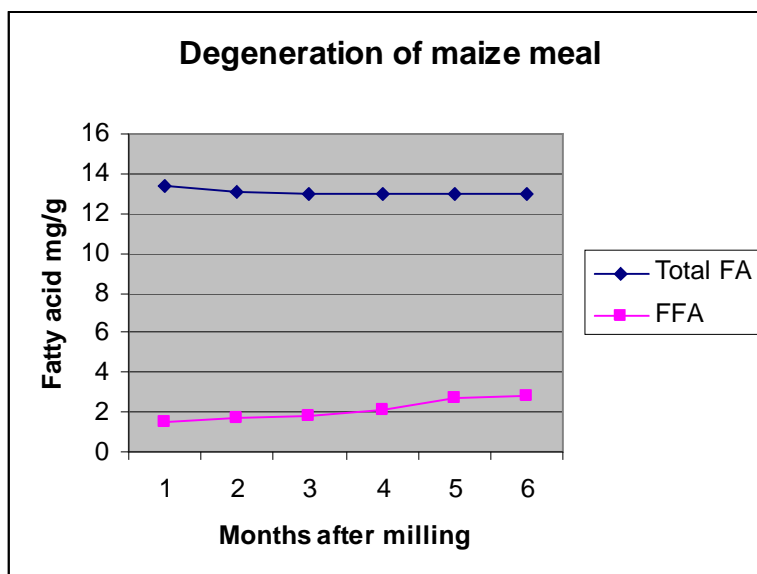
Cereals have different patterns of degeneration. Most can be stored for long periods under suitable conditions. In Africa all the main cereal staples – millet, sorghum, wheat and maize, can be stored as whole grain without apparent problems. The storage of milled products is variable. Rancidity develops relatively quickly with both **sorghum** and **millet** flour. They become unpalatable within a short time. Firstly triglyceride fatty acids are de-esterified, then the fatty acids themselves are broken down. The first stage does not have major effects on taste, in fact may enhance taste to some extent. The second stage of fatty acid breakdown results in rancidity, and the flour is uneatable. The drier and less humid the storage, the longer the milled product can survive. With sorghum and millet in the African setting of warmth and humidity, this time is measured in days. For **wheat** in cool dry climates, and with sealed storage, neither stage proceeds at any great pace, and flour may still be useable after many years (Greer et al 1954). In good conditions the first stage of degeneration is measureable in that there is a significant presence of free fatty acid in the flour, but

hardly any loss of total fatty acid, indicating that there has been no further breakdown of the free fatty acids, and therefore no rancidity

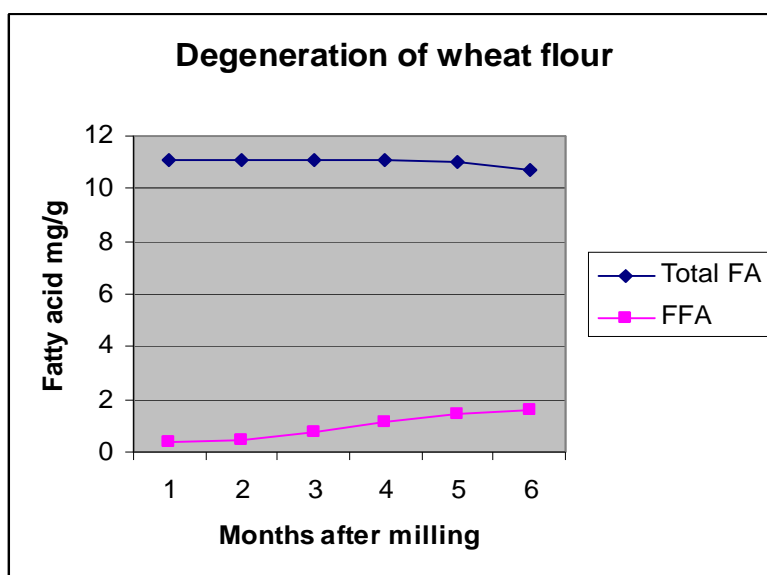
maize meal undergoes a significant deesterification of its fatty acids. Up to 42% of the fatty acids may be in the free form
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(See figures below). In poorer conditions, both stages proceed: there is significant freeing of fatty acids from their esterification, and significant further breakdown to products that will eventually render it uneatable (Lopez and Vidal-Quintanar 2000).

**Maize** meal undergoes a significant deesterification of its fatty acids. Up to 42% of the fatty acids may be in the free form (Sammon 1999). This process begins within the first weeks of milling. While both maize and wheat retain their palatability for many months or even years, we have shown (Figure 1) that in maize there can be very high deesterification of fatty acids without accompanying further degeneration and subsequent rancidity.



**Degeneration of maize meal at room temperature measured monthly by High Resolution Gas Chromatography** (Sammon AM, Gloucester Royal Hospital; and Whittington FM, University of Bristol). At six months 0.6% of the total fatty acid had been lost.



**Degeneration of wheat flour at room temperature measured monthly by High Resolution Gas Chromatography** (Sammon AM, Gloucester Royal Hospital; and Whittington FM, University of Bristol). At six months 3.5% of the total fatty acid had been lost.

In this study there was a significantly higher deesterification with maize than with wheat, and significantly less loss of total fatty acid. This study suggests

maize meal remains palatable despite very major chemical change

that maize meal remains palatable despite very major chemical change. This applies less to wheat, since deesterification of wheat was paralleled by loss of total fatty acid, signalling degeneration of the free fatty acids to products which would unfavourably alter taste. The health dangers of a large quantity of non-esterified fatty acids carry a



taste warning with sorghum and millet, much less with wheat, and almost none with maize.

## Discussion

Inconsistency exists between the history of maize as a monocrop in parts of Africa and that of SCO. The sudden rise of SCO in the 1930s to 1950s in some parts of East and Southern Africa was not accompanied by an equivalent rise in total maize use, nor do the countries with the greatest maize use suffer the greatest SCO incidences. The rise in SCO did not parallel the rise in deficiency diseases associated with maize as monostaple, which were severe in the late 19th century and early 20<sup>th</sup> century. It is reasonable to examine major changes that occurred in the 1930s to find aetiological evidence. The change to white maize was relatively slow, and the dietary

suddenly, in the early 1930s, a 'new' food has become available to the great majority of people – and this is when the rise in SCO begins

consequences apparently not great enough to cause a sudden rise of SCO of epidemic proportions. Maize meal, the one preparation of maize with a proven high risk association with SCO

became rapidly more available over the decades following the introduction of the small-scale hammer mill. If maize meal is a prime agent in the aetiology of SCO then this piece of technological history is critical.

The degenerative pattern of maize meal is distinct from whole grain maize, and quite different from millet and sorghum flour. The characteristics of maize which has been milled some weeks or months before are markedly different from fresh, home-ground maize. Suddenly, in the early 1930s, a 'new' food has become available to the great majority of people – and this is when the rise in SCO begins.

## Conclusion

Maize is associated with SCO in Africa. The association began well after maize had become a major source of calories in many parts of the continent, and coincided with a continued growth in maize use, but also with sudden widespread availability of machine-milled maize. The closest association of SCO is with maize meal, and this has been shown in both Africa and Italy. The association has a linear association with dose of maize meal.

Maize meal, of all cereal flours, has the property, on storage, of high percentage de-esterification of fatty acids without development of rancidity.

## 9 Maize, linoleic acid and prostaglandin E2.

### Chapter summary

A maize-based, otherwise poor diet has a very high omega-6 to omega-3 fatty acid ratio, and because of this, increases PGE2 production throughout the body, including the gastric mucosa. Linoleic acid in esterified form mediates a slow sustained production of PGE2. Nonesterified linoleic acid causes a rapid and temporary increase of PGE2 production in the gastric mucosa.

There are significant effects of intragastric PGE2 on upper GI function including acid suppression and upper GI reflux. These same effects are produced by maize consumption: the slow effects by a maize-based diet, the rapid effects by maize meal. PGE2 is also directly mitogenic to the oesophageal mucosa.

### Chapter content

#### Diet and production of prostaglandins

#### Upper GI and prostaglandins

#### Upper GI prostaglandins – slow effects and immediate effects

#### Maize – slow effects

#### Maize – immediate effects

#### Discussion

#### Conclusion

#### Diet and production of prostaglandins

A diet high in omega-6 and low in omega-3 fats is regarded as a health hazard for those in rich countries. In western countries the ratio of omega-6 to omega-3 is currently about 10:1. A ratio of 2:1 has been recommended (Simopoulos et al 1999).

recommended dietary omega-6: omega-3 ratio is 2:1 Ratio in maize is up to 83: 1
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The dietary balance of omega-3 and omega-6 fatty acids determines the composition of body and plasma fat (Dougherty et al 1987; Chan et al 1993; James et al 1993) and the balance of prostaglandins produced in the body.

High dietary intake of the omega-6 fat linoleic acid results in a high production of PGE2 in the body (Schepp et al 1988; Marshall et al 1983; Bunce et al 1992; Blair et al 1993; Alam et al 1991; Wander et al 1997; Rayon et al 1997). A small increase in omega-3 is more effective in combating this than a reduction in omega-6 (Raedersdorff and Moser 1992).

the dietary balance of omega-3 and omega-6 fatty acids determines the balance of prostaglandins produced in the body

This has been demonstrated in Africa: salivary PGE<sub>2</sub> was measured in a group of subjects on very low dietary fat in Transkei. Their small amount of dietary fat came from maize of which the fat is principally linoleic acid (omega-6). PGE<sub>2</sub> in the saliva was more than 3 times that of Transkeians on a medium fat diet, and more than 7 times that of UK subjects (Sammon and Morgan 2002).

Certain dietary deficiencies affect prostaglandin production:

Riboflavin deficiency increases biosynthesis of PGE<sub>2</sub> in rat kidneys (Pelliccione et al 1985).

Vitamin E deficiency promotes PGE<sub>2</sub> production in rats (Hope et al 1975; Eskew et al 1989; Meydani et al 1985).

Selenium is involved in and necessary for normal regulation of prostaglandin synthesis (Capdevila et al 1995). Deficiency promotes the production of PGE<sub>2</sub> in rat alveolar macrophages (Eskew et al 1989) and its secretion by bovine mammary cells (Maddox et al 1991; Cao et al 2000).

Thus a diet deficient in vitamins and minerals may be a further influence on production of PGE<sub>2</sub>.

## Upper GI and prostaglandins

There are distinct local effects of diet on the upper gastrointestinal tract.

Increased dietary linoleic acid results in increased intragastric production of PGE<sub>2</sub> (Schepp et al 1986; Schepp et al 1988; Cargille et al 2004), and this increase has known effects:

PGE<sub>2</sub> causes duodenogastric reflux in healthy men

- 1 PGE<sub>2</sub> relaxes the lower oesophageal sphincter (Diliwari et al 1975; Mukhopadhyay et al 1975; Goyal et al 1973).
- 2 PGE<sub>2</sub> relaxes the pylorus (Milenov et al 1982; Mishima et al 1976; Hausken et al 1991).
- 3 PGE<sub>2</sub> causes duodenogastric reflux in healthy men. Antral contractions are decreased (Dooley et al 1985).
- 4 PGE<sub>2</sub> reduces acid secretion (Konturek et al 1980).

PGE<sub>2</sub> has also been shown to promote oesophageal cancer by Shimizu (1986). In his study, PGE<sub>2</sub> administration to rats caused oesophageal papillomas, dysplasia and oesophageal carcinoma. Pink (2005) has shown a mitogenic effect of PGE<sub>2</sub> on oesophageal mucosa cells.

## Upper GI prostaglandins - slow effects and immediate effects

There are two types of dietary effect on prostaglandin function in the upper GI tract:

### a Slow and low and sustained

In rats, dietary supplement with linoleic acid in corn (maize) oil (10% of dietary energy) increased intragastric PGE<sub>2</sub> threefold, and reduced basal and stimulated acid production. This was measured over 8 weeks (Schepp et al 1988).

Cargille et al (2004) showed the same long-term effect with ponies where corn oil supplement (45ml daily) resulted in raised intragastric PGE<sub>2</sub> and decreased gastric acid output over five weeks.

Grant et al (1988) gave healthy human subjects 1.5G or 3 G daily of linoleic acid for 2-3 weeks and found an increase in intragastric PGE<sub>2</sub> and a fall in the maximal gastric acid output.

### **b Fast and high and temporary**

The linoleic acid in whole maize and in corn oil is esterified as triglyceride, and most of that is absorbed as triglyceride from the stomach. Free fatty acids rather than esterified fatty acids are the direct substrates for prostaglandin synthesis (Samuelson 1970). They

free fatty acids rather than esterified fatty acids are the direct substrates for prostaglandin synthesis

act quickly and at low dose. Non-esterified linoleic acid is converted to arachidonic acid and then to PGE2 in the gastric mucosa (Nakaya et al 2001).

Intragastric administration of arachidonic acid to rats results in a rapid increase of PGE2 concentration in the gastric lumen of 5000 to 13000 times (Hollander et al 1982).

Intragastric free linoleic acid provides immediate protection against ethanol damage in rats (Tarnawski et al 1987). They gave 74 mg doses of linoleic acid to rats, and this was protective against an ethanol challenge given an hour later. Intrajejunal administration of linoleic acid was not effective. They concluded that this was a local, topical effect mediated by prostaglandin production.

### **Maize – slow effects**

Linoleic acid constitutes up to 68.8% of the fatty acids of maize (Jahn Deesbach 1975). It may have an n-6 to n-3 ratio of fatty acids of up to 83:1 (Dupont et al 1990). This fat is almost all bound in triglyceride form. Only 0.3% of fatty acids are non-esterified in maize seed at 90 days after pollination (Weber 1969).

Fatty acids are intentionally neutralised during refining of maize oil and free fatty acids are typically 0.05, with a specification of <0.1% (Maizola, personal communication).

corn (maize) oil shows all the type a effects- slow and low and sustained

Corn (maize) oil shows all the type a effects:

Corn Oil raises PGE2 in rat lungs (Rayon et al 1997).

Rats fed corn oil had higher plasma PGE2 levels than others (Bunce et al 1992).

Dietary corn oil raises PGE2 in liver and serum in rats (Marshall et al 1983).

Corn oil dietary supplementation significantly decreases acid output and significantly increases PGE2 in the stomach in ponies (Cargile et al 2004).

Corn oil lowers the peak pressure of the lower oesophageal sphincter in man (Nebel and Castell 1973).

One of the principal effects of PGE2 in the stomach is suppression of acid production. In Transkei in a rural community a bimodal distribution of intragastric pH has been demonstrated. Half of a rural sample population was found to have a fasting intragastric pH of over 4. A high pH was significantly associated with consumption of maize (Sammon et al 2003).

### **Maize – immediate effects**

Stored maize meal can contain a high level of non-esterified linoleic acid. After six months of storage in a temperate climate this has been measured at 163mg/100gram maize meal (Sammon and Whittington –see figure 1, previous chapter), and after prolonged storage has been measured at 363mg/100g sample of maize meal (Sammon and Morgan 2002). This is equivalent to an intake of over 1 gram daily of non-esterified linoleic acid in a principally maize meal based diet.

In man, lipase is produced in the gastric fundus (Moreau et al 1988), providing another, probably minor, source of non-esterified fatty acid within the stomach lumen. Maize meal shows some type b effects. Regurgitation is very common in Transkei, and occurs particularly in response to two maize meal-based foods: *umqa* (maize/pumpkin mash) and *amarewu* (non-alcoholic fermented maize drink). (See chapter 8) 60% of a random sample of Transkeians suffered from heartburn, often very extensive in severity and extent. Regurgitation of bile was common. Aspirin, a prostaglandin inhibitor, diminished or abolished this heartburn, providing evidence that the heartburn is a prostaglandin-mediated effect (Sammon 1994).

maize meal shows some type b effects - fast and high and temporary

Fresh maize oil from home-pounded maize was strongly ulceroprotective in rats (Tovey et al 2005). Commercial corn oil was not. Commercial corn oil (see above) is treated to reduce free fatty acids to a maximum of 0.1%. No such treatment was applied to the corn oil produced freshly, and a prime candidate for the effect found is a small quantity of non-esterified linoleic acid, with its proven ulceropreventive ability.

## Discussion

Raised PGE2 in the stomach is a direct effect of a high-maize diet. It is probable that the microdeficiencies of a maize-based diet also swing the preponderance to PGE2.

The evidence is of a strong diet-driven bias towards preferential production of PGE2 in rural Africa, that this bias produces predictable and measureable physiological results, and that these physiological changes are sufficient to cause profound changes in upper GI function and susceptibility. Maize meal contains a high level of non-esterified linoleic acid, and produces symptoms typical of a rapid and high PGE2 response to free linoleic acid.

these physiological changes are sufficient to cause profound changes in upper GI function and susceptibility

There are two potential carcinogenic mechanisms – a direct mitogenic effect of PGE2, and a diet mediated duodenogastro-oesophageal reflux.

## Conclusion

A maize-based diet in rural Africa has major effects on prostaglandin production throughout the body, and locally in the upper gastrointestinal tract. Excess PGE2 is produced which causes major physiological abnormalities in the upper gastrointestinal tract.

## **10 Foods II – other foods**

### **Chapter summary**

Alcohol is not a risk factor in endemic areas for SCO.

Vitamins and mineral supplements have usually been given in combinations. The one micronutrient that passes the tests of proven deficiency in endemic areas - significant lower levels in SCO victims, and significant improvement on supplement is deficiency of selenium. Lower level evidence exists against deficiencies of riboflavin, vitamin E and beta-carotene.

*Solanum nigrum* and lima beans have evidence of a positive association with SCO from a single case-control trial only, but both have the possibility of being major aetiological factors since they have highly significant associations. Pumpkin also has scanty evidence as an aetiological agent except as part of the Transkei diet of maize, pumpkin and beans, but a significant association may be present.

The protective value of dietary fat is strongly supported by two case-control studies in very high risk areas.

Fresh fruit and vegetables have evidence of a protective effect worldwide, but inconsistent evidence in high-risk areas.

### **Chapter content**

**Alcohol**

**Vitamins and minerals**

**Wild herbs**

**Fats**

**Fruit and vegetables**

**Beans**

**Pumpkin**

**Opium**

**Discussion**

**Conclusion**

**Alcohol**

As noted in chapter 2, there is a well-established linear dose-related association between alcohol consumption and oesophageal cancer in low and medium-incidence countries.

Cook (1971) demonstrated a geographical link between maize beer and CO in Africa. Alcoholic drinks were blamed in Transkei by Burrell, who described 'fortified bantu beer' prepared in discarded metal drums containing petroleum asphalt. Added to the brew are 'carbide, liquid metal polish etc. to give it an additional kick' (Burrell et al 1966; Burrell 1957). The idea was so attractive that it greatly outlasted its scientific credibility.

### **Alcohol in high risk areas**

There are two reports from regions near the endemic area of Linxian in China: In Huaian, China, a high-risk region for SCO, alcohol abstinence was significantly protective (Wang et al 2006).

In Yanting, Sichuan Province, China, a high risk area, a case-control study was carried out. There was a significant association between alcohol consumption and oesophageal cancer (Yang et al 2005).

Similarly there are two reports from near the endemic region of Transkei (See chapter 6). Frequent alcohol consumption caused a marginally increased risk for oesophageal cancer: an Odds Ratio of 1.7 for women and 1.8 for men in greater Johannesburg (Pacella-Norman et al 2002).

Segal et al (1988) however, found a significant risk associated with alcohol consumption in Soweto (within Greater Johannesburg). Their results are discordant with Pacella-Norman et al's results. Segal et al's controls were from a significantly different social grouping from the SCO patients. The results, certainly in terms of the consumption of alcohol, are open to question.

### **Endemic areas**

Several studies have concluded that alcohol is not a risk factor in endemic areas for CO (Rose 1982; Munoz et al 1982).

In Linxian, in a case-control study of oesophageal and gastric cardia cancers (SCO 30%, adenocarcinoma 17%, unknown 52%) less than 4% of the patients had ever been at least occasional drinkers of alcohol (Li et al 1989).

In the Linxian Nutrition Intervention Trial, Guo et al (1994) report on a nested

several studies have concluded that alcohol is not a risk factor in endemic areas
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case-control study of 640 patients from the high risk area who developed oesophageal cancer subsequent to enrolment in the study. Alcohol consumption was uncommon and was not related to risk of SCO.

Two further reports confirm that in Linxian people do not drink much alcohol, and there is no association between SCO and alcohol (Department of Epidemiology of CICAMS 1977; Tran et al 2005).

The Joint Iran-International Agency for Research on Cancer Study Group (1977) found that less than 10% of men drank alcohol in the high risk area of Iran. Less than 1% were even moderate drinkers by western standards. In the villages alcohol was unobtainable. They concluded that alcohol is not a significant factor in development of SCO in Iran.

Most studies in Africa show that a significant percentage of SCO patients do not consume alcohol. It is important to note that Cook's observation was of a link between maize as major content of beer and CO, not alcohol and CO (Cook 1971).

In a high incidence area of Zimbabwe (crude annual incidence of 93.9 for males), case-control analysis showed no independent effect of alcohol consumption on the risk of oesophageal cancer (Parkin et al 1994).

There is an apparent lack of appreciable effects of alcohol usage on the disease in

alcohol is a risk factor in all areas except truly endemic
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Zulus (van Rensburg et al 1985a).

A case-controlled study in Transkei showed no association between consumption of Xhosa beer and oesophageal cancer (Sammon 1992). Matsha et al (2006b) also showed that in Transkei home brewed beer is not a risk factor for SCO.

The evidence is that alcohol is a risk factor in all areas except truly endemic.

This poses the question as to why alcohol is not a risk factor in endemic areas. In Linxian and Iran there is very little alcohol consumed, but that is not the case in Transkei.

### **Actions of alcohol:**

Alcohol increases gastro-oesophageal reflux through lowered sphincter pressure. Relatively modest quantities of alcohol induce gastro-oesophageal reflux in healthy people (Kaufman and Kaye 1978).

At low dose, it increases acid production, and at higher dose reduces acid secretion by damaging the mucosa (Mc Math 1990).

It decreases the concentration of trypsin and chymotrypsin in the stomach (Skrzydowska et al 1989).

It increases plasma gastrin (Hajnal et al 1990).

It increases pepsinogen secretion (Puurunen et al 1982).

Alcohol interferes with prostaglandin synthesis: it suppresses salivary secretion of PGE2 (Wu-Wang et al 1991).

Alcohol causes or accentuates dietary deficiencies of vitamins and minerals (van Rensburg 1981; Wynder and Stellman 1977).

McSween (1982) adds that alcohol may act as a solvent for the carcinogens of tobacco, and/or may itself contain contaminant carcinogens.

Alcohol is the biggest known risk factor in low and medium incidence areas. The risk is strong – Relative Risk over 5 in low and medium risk areas (Yu et al 1988; Tavani et al 1994; Pottern et al 1981; Tuyns et al 1983) - and is dose-related.

It is an additive risk factor in Italy with maize meal.

In Italy R R for tobacco is up to 2.93 (daily consumption of 11-20g), for alcohol up to 13.08(daily consumption of over 120g), maize meal up to 6.17 (daily consumption of over 106g). All are dose related. Alcohol and maize meal are additive in their effect. In Italy, maize only increases the risk if the alcohol consumption is high (Franceschi et al 1990).

### **Possible explanations:**

A Alcohol does exactly the same as the ‘endemic factor’. When the endemic factor is fully expressed then alcohol has nothing to add. This could be through any combination of:

- 1 Promotion of gastro-oesophageal reflux
- 2 Gastric acid suppression
- 3 Trypsin inhibition
- 4 Creation of nutritional deficiencies which predispose to carcinogenesis



B Alcohol is antagonistic to the endemic factor. However in no trial has there been demonstrated a negative effect of alcohol, either in small or large quantities.

C The endemic factor mechanism protects against alcohol damage. Arachidonic acid protects the gastric mucosa against ethanol injury (Hollander et al 1982). Linoleic acid is its precursor, and its predominant presence in maize may negate the effects of alcohol on the oesophagus as well as the stomach. Maize oil does protect against the effects of alcohol in the stomach (Tovey et al 2005).

## Vitamins and Minerals

Van Rensburg (1981) blames micronutrient deficiency for high incidences of SCO. He found markedly lower levels of serum magnesium and carotene in a very high-risk area for SCO than in a moderate risk area (van Rensburg 1983).

Yang et al (1984) reported deficiency of vitamins A and E, and beta-carotene in the high-risk population of Linxian.

Yang (1980) reports an inverse relationship in Northern China between SCO mortality and hair content of magnesium, molybdenum and zinc.

Jackson (1952) reported a high level of malnutrition in Transkei in 1952.

He found that riboflavin deficiency was much more common than pellagra.

In rats given oesophageal carcinogens, supplementing marginally deficient corn or wheat diets with various combinations of nicotinic acid, riboflavin, zinc, magnesium, molybdenum and selenium significantly reduced the number of oesophageal tumours (van Rensburg et al 1985). Riboflavin and molybdenum also reduce the incidence of stimulated rat oesophageal cancers (Bespalov et al 1990).

A very great deal of information is available from the Linxian Nutrition Intervention Trial. The general population trial involved 29,584 Linxian residents who were randomised to receive

a 42% reduction in oesophageal cancer prevalence in those taking beta-carotene, vitamin E and selenium, but this was not statistically significant
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a) retinol and zinc; b) riboflavin and niacin; c) vitamin C and molybdenum; d) beta-carotene, vitamin E and selenium. The first part of the trial was for 5.25 years. There was no statistically significant reduction in prevalence of oesophageal or gastric cancer for any of the four interventions. There was a significant reduction in total mortality, and in prevalence of gastric cancer in the group which received retinol and zinc (Blot et al 1993). They reported no significant reduction in oesophageal cancer. Taylor et al (1994) reported, from the same trial, a 42% reduction in oesophageal cancer prevalence in those taking beta-carotene, vitamin E and selenium, but this was not statistically significant.

Also providing much information is the Dysplasia Trial in Linxian. 3318 Linxian Residents with cytological evidence of oesophageal dysplasia received daily supplements of multiple vitamins and minerals. At 2.5 and 6 years repeat cytology was carried out. There was no significant reduction in prevalence of SCO. There was a significant increase in reversion to non-dysplastic cytology in the treatment group. (Mark et al 1994).

In China supplement with multivitamins and minerals was accompanied by 'a minor reduction in vertical distribution of labelled' cells which was seen as an improvement (Rao et al 1994).

In China, supplement with riboflavin, retinol and zinc reduced micronuclei in oesophageal cells (Munoz et al 1987).

In Transkei Jaskiewicz et al (1987b) found a reduction in cellular atypia after the summer months in Transkei. These changes could not be reproduced by supplementation with deficient micronutrients.

### **Niacin (Nicotinic acid)**

Pellagra, the disease of niacin deficiency, is strongly associated with a maize-based diet. Nicotinic acid is present in maize but in a bound form. It can be released by alkaline treatment such as the South American process of nixtamalisation - in South America there is very little pellagra.

Pellagra increased tremendously in some areas in South Africa after 1930 (Warwick and Harington 1973). Gillman and Gillman (1948) described an increase of pellagra in the 1940s as 'alarming'.

Groenewald et al (1981) in a dietary questionnaire found a high frequency of inadequate intake of niacin in Transkei.

The Joint Iran-International Agency for Research on Cancer Study Group (1977) found adequate intake of niacin in the high incidence areas of Iran, and a higher intake in the high incidence areas than in other areas.

Siassi et al (2000) found a doubling of the risk of oesophageal cancer in those with a low intake of niacin in the high incidence area of Iran.

Neither the Intervention Trial nor the Dysplasia Trial in Linxian showed any benefit of long-term niacin supplementation.

### **Vitamin A**

Riboflavin and vitamin A deficiency are characteristic of regions of highest incidence (Ghadirian et al 1988).

Vitamin A levels in plasma were lower in Transkei/Ciskei people with oesophageal dysplasia or malignancy (Jaskiewicz et al 1988).

Yang et al (1984) reported deficiency of vitamin A in the high-risk population of Linxian.

Thurnham et al (1982) found 5% of their sample population in Linxian had deficient vitamin A status.

Hormozdiari et al (1975) found a low intake of vitamin A in the high incidence area of Iran.

A randomised double-blind study in Huixian, China, giving retinol, riboflavin and zinc found a significant reduction in prevalence of micronuclei in oesophageal cells in the treatment group (Munoz et al 1987). The authors did not confidently attach to this a significant association with oesophageal carcinogenesis. There was no reduction in pre-cancerous oesophageal lesions (Munoz et al 1985).

Wang et al (1994) reported from the Linxian Nutrition Intervention Trial a non-significant reduction in gastric cancer prevalence for those randomised to retinol and zinc. There was no effect on SCO.

### **Vitamin E**

Yang et al (1984) reported deficiency of vitamin E in the high-risk population of Linxian.

Jaskiewicz et al (1988) found lower levels of vitamin E in blood of patients presenting with dysplasia or malignancy than in those with normal cytology, and those in low risk areas.

Vitamin E, with beta-carotene and selenium, given to one group of the intervention trial in Linxian, showed a non-significant trend towards reduction in SCO prevalence (Taylor et al 1994).

### **Beta-carotene**

Yang et al (1984) reported deficiency of vitamins A and E, and beta-carotene in the high-risk population of Linxian

Thurnham et al (1982) in their study of 111 Linxian inhabitants found normal plasma carotene levels.

Van Rensburg et al (1983) found markedly lower levels of serum magnesium and carotene in a very high-risk area for SCO than in a moderate risk area.

Taylor et al (1994) reported, from the Linxian Nutrition Intervention Trial a 42% reduction in oesophageal cancer prevalence in those randomised to take beta-carotene, vitamin E and selenium; this was not statistically significant.

### **Riboflavin**

Riboflavin and vitamin A deficiency are characteristic of the regions of highest incidence in the world (Ghadirian et al 1988).

The Joint Iran-International Agency for Research on Cancer Study Group (1977) found a much lower intake of vitamin A, riboflavin and vitamin C in the high incidence areas of Iran.

Groenewald et al (1981) in a dietary questionnaire found a high frequency of inadequate intake of riboflavin in Transkei.

Jackson (1952) reported a high level of malnutrition in Transkei. He found that riboflavin deficiency was much more widespread than pellagra.

In Linxian, China, a study of 105 patients undergoing endoscopy found 96% deficient in riboflavin (Munoz et al 1982).

Yang et al (1984) found 90% of a sample population in Linxian riboflavin deficient.

Munoz et al (1982) found low riboflavin in 96% of an at-risk population in Linxian.

Thurnham et al (1982) found that 97% of a sample of Linxian inhabitants had low plasma riboflavin.

There is low intake of riboflavin in high incidence villages of the Caspian Littoral area of Iran (Hormozdiari et al 1975). Siassi and Ghadirian (2005) reported that in high incidence areas of Iran, riboflavin intake is lower than in control regions, and that the households of SCO patients had significantly lower riboflavin intake than control households. However a case-control study by Siassi et al (2000) in the high-risk area of Iran did not find an association between riboflavin level and SCO patients and their relatives compared to healthy controls.

Foy showed that a pure riboflavin deficiency raises the mitotic rate of oesophageal mucosa in baboons
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In addition to the known riboflavin deficiency signs of cheilosis, glossitis, burning lips and tongue, pure riboflavin deficiency produces a pseudocarcinomatous hyperplasia of oesophageal mucosa in baboons (Foy and Kondi 1984).

Foy et al (1964) and Foy (1972) showed that a pure riboflavin deficiency raises the mitotic rate of oesophageal mucosa in baboons.

In rats given carcinogens, supplementing marginally deficient maize or wheat diets with various combinations of nicotinic acid, riboflavin, zinc, magnesium, molybdenum and selenium significantly reduced the number of oesophageal tumours (van Rensburg et al 1985b).

Foy and Kondi (1984) report on 11 baboons fed a balanced diet, but without riboflavin. They developed lesions of the skin, mouth and oesophagus. In the oesophagus this was gross hyperplasia with numerous mitotic figures.

In the Linxian Nutrition Intervention Trial diet supplement with riboflavin brought no improvement in cancer mortality (Blot et al 1993).

A randomised double-blind study in Huixian, China, giving retinol, riboflavin and zinc found a significant reduction in prevalence of micronuclei in oesophageal cells in the treatment group (Munoz et al 1987). The authors, as noted above, did not confidently attach to this a significant association with oesophageal carcinogenesis. There was no reduction in precancerous oesophageal lesions (Munoz et al 1985).

The above findings differ from those of Ding et al (1999) who randomised 3393 patients with mild dysplasia to receive riboflavin or placebo. At five years there was no significant difference, but at 9 years the malignant transformation rate was significantly decreased.

Lin et al (1988) randomised 2411 patients with mild oesophageal dysplasia to receive placebo or riboflavin. At about three years they were re-examined and the prevalence of SCO found to be 19% less in the treatment group.

The evidence available suggests that riboflavin may have a marginal role in the aetiology of oesophageal cancer in endemic areas.

### **Selenium**

Most selenium in maize is present as selenomethionine and not easily accessible on digestion (Beilstein et al 1991). Selenium levels are lower in susceptible populations in China (Li 1991) and in South Africa (Jaskiewicz et al 1988) than in surrounding less susceptible populations. A study of population selenium levels in Iran did not find any such association (Nouarie et al 2004).

Those with malignant or pre-malignant cytology have lower levels of selenium - an inverse association was found with SCO and cytological abnormalities in a high oesophageal cancer area of South Africa (Jaskiewicz et al 1988).

The plasma selenium level is significantly related to cancer risk in Transkei with lower levels found in those with cytological abnormalities (Jaskiewicz et al 1989).

selenium level is significantly related to cancer risk in Transkei
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Erythrocyte selenium levels were lower in subjects with severe oesophageal dysplasia and in oesophageal cancer patients than in normal subjects in China (Li 1991).

In rats subjected to oesophageal carcinogens, a supplement with selenium resulted in a significantly reduced oesophageal cancer load (Bogden et al 1986).

The Linxian Nutrition Intervention Trials showed a non-significant trend to reduction in prevalence of oesophageal cancer in those randomised to receive beta-carotene, vitamin E and selenium (Taylor et al 1994).

### **Zinc**

Zinc deficiency increases the yield of cancers of the oesophagus in rats and mice given oesophageal carcinogens (Fong et al 1996; 1997; 2003a; 2003b).

There are studies which show some association between oesophageal cancer patients and a lower zinc level in non-endemic areas (Lipman et al 1987; Rogers et al 1993; Lu H et al 2006).

There is low zinc in endemic areas. Thurnham et al (1982) reported that 24% of Chinese in a survey of 111 subjects in Linxian had low plasma zinc compared with subjects in Denver.

Yang (1980) reports an inverse relationship in Northern China between SCO mortality and hair content of magnesium, molybdenum and zinc

In China, supplement with riboflavin, retinol and Zinc reduced micronuclei in oesophageal cells (Munoz al 1987).

Van Rensburg et al (1983) showed a low 'though not necessarily deficient' level of zinc in blood of 27% of subjects from a high-risk area of Transkei.

The Linxian Nutrition Intervention Trial showed a non-significant (P=0.09) reduction in gastric cancer for those on retinol and zinc (Wang et al 1994).

A randomised double-blind study in Huixian, China, giving retinol, riboflavin and zinc found a significant reduction in prevalence of micronuclei in oesophageal cells in the treatment group (Munoz et al 1987). The authors did not confidently attach to this a significant association with oesophageal carcinogenesis. There was no reduction in precancerous oesophageal lesions (Munoz et al 1985).

Jaskiewicz et al (1989) found no association in Transkei between high incidence areas for SCO and zinc on a regional or a personal basis.

### **Molybdenum**

Burrell et al (1966) reported molybdenum deficiency in the gardens of SCO victims in Transkei (see chapter 7).

Yang (1980) reported an inverse relationship in Northern China between SCO mortality and hair content of magnesium, molybdenum and zinc.

Vitamin C and molybdenum brought no reduction in SCO incidence in the Linxian Nutrition Intervention Trial (Taylor et al 1994).

In the rat oesophagus riboflavin and molybdenum reduced the incidence of carcinogen-related cancers (Bespalov et al 1990).

### **Magnesium**

Van Rensburg et al (1983) found markedly lower levels of serum magnesium and carotene in a very high-risk area for SCO than in a moderate risk area.

Yang (1980) reports an inverse relationship in Northern China between SCO mortality and hair content of magnesium, molybdenum and zinc.

Jaskiewicz et al (1989) found no association in Transkei between high incidence areas for SCO and magnesium on a regional or a personal basis.

### **Wild Herbs**

There is a vast array of wild plants that are used in Africa to supplement the diet.

Transkeians use many of these (Rose and Guillardmod 1974). *Umsobo* (*Solanum nigrum*) is one of very many. (See image at

[http://commons.wikimedia.org/wiki/File:Solanum\\_nigrum.jpg](http://commons.wikimedia.org/wiki/File:Solanum_nigrum.jpg)).

*S. nigrum* is common in Transkei. The leaves are used as a potherb. Leaves are also dried in the autumn, and ground for cooking out of season. The fruit may also be used in cooking (Lubbe 1973). Its morphology varies with its location and soil (Rose 1974).

Schutte (1966) reported that compared to plants in good soil, molybdenum deficient *S. nigrum* plants have an erect growth, flower early and give a very good yield of fruit; the plants differed in leafiness, shape of leaf and in the hairiness of the stem. Yet 'both looked healthy and vigorous. There was no indication of any deficiency symptom'. Rose and Guillarmod (1974) wrote that 'it is so universally used that apart from possible difference in genetic composition one must consider whether the same conditions which appear to influence morphology may in fact determine toxicity'.

*Solanum nigrum* has recorded actions:

A study of the plant by Akhtar and Munir (1989) found that *Solanum nigrum* extract decreased the ulcer index in rats significantly. Pepsin levels were very significantly reduced by the methanolic extract. Powdered *S. nigrum* had greater pepsin binding capacity than its extracts. He concluded that the antiulcer action of *S. nigrum* could be due to a decreased output of acid and pepsin. 'This plant drug seems not to act by strengthening the mucosal defence but by weakening aggressive factors like gastric acid and pepsin by way of decreasing their glandular secretion and also by directly binding to them'.

a carcinogen was certainly present in the food

due to a decreased output of acid and pepsin. 'This plant drug seems not to act by strengthening the mucosal defence but by weakening aggressive factors like gastric acid and pepsin by way of decreasing their glandular secretion and also by

*S Nigrum* fruit contains acetylcholine (De Melo et al 1978).

Rats fed the full Transkei diet of maize beans and salt, including fresh *S. nigrum* and *S. oleraceus* developed severe liver lesions and epithelial cell dysplasia of the oesophagus. Those which had only maize, beans and salt did not. The authors concluded 'A carcinogen.... was certainly present in the food' (Purchase et al 1975).

Either *Solanum nigrum* or *Sonchus oleraceus* contains a mutagen. *Sonchus oleraceus* leaves are used as salad in Mediterranean countries, and there are no reports of carcinogenic activity, which casts considerable concern on *S. nigrum*.

there is a vast array of wild plants that are used in Africa to supplement the diet

Rose (1982) noted that *Solanum nigrum* is eaten in high incidence areas but not in low incidence areas.

Burrell et al (1966), writing about the gardens of those families who had an SCO victim '... the occupants of cancer gardens depend more on pumpkin vine tips and 'edible' weeds than do the occupants of tumour free gardens'.

My own case-control study in Transkei found a very strong association between *S. nigrum* and SCO. 89% of SCO patients and 77% of controls consumed it. The relative risk for users was 3.6 (Sammon 1992).

## Fats

A French dietary study identified butter as a positive risk factor for oesophageal cancer (Launoy et al 1998). Tuyns (1987) however, also in France, found animal proteins and polyunsaturated fatty acids were found to be protective, also fresh meat, citrus fruit and oil.

This is contrary to findings in endemic areas for SCO - butter or margarine daily was protective against SCO - a Relative Risk of 0.51 for CO in Zulus (van Rensburg et al 1985a). Similarly in a case-control study in Transkei a higher total intake of bought fat was protective (Sammon 1992).

## Fruit and vegetables

There is a known association in USA and in Europe of CO with a low intake of fruit and green vegetables (Pottern et al 1981; Yu et al 1988; Tavani et al 1996; Boeing et al 2006; Terry et al 2001; Tuyns et al 1987).

In a 65-county study in China of food consumption esophageal cancer was associated with a diet 'rich in starchy tubers and salt, lack of consumption of meat, eggs, vegetables and rice' (Zhou and Watanabe 1999).

Hormozdiari et al (1975) found a low intake of fresh vegetables and fruit was associated with SCO in the high incidence area of Iran.

Cook-Mozaffari et al (1979) found a strong association with a low intake of fruit and vegetables in a case-control study in the Caspian Littoral of Iran.

Yang et al (2005) in a high-incidence area for SCO in China found fresh fruit significantly protective, and fresh vegetables showed a trend towards being protective. The Linxian Nutrition Intervention Trial nested case-control study by Guo et al (1994) reported high consumption of eggs or fresh vegetables as associated with a 20% reduction in SCO risk.

Li et al (1989), in a case-control study of cancers of the oesophagus and gastric cardia in Linxian found no association with intake of fruit and fresh vegetables.

Jaskiewicz et al (1988) found that green vegetables and fruits were eaten less often in high-risk areas for SCO in Transkei and Ciskei.

No association with fruit and vegetables was found in van Rensburg et al's case-control study in Zulu men (1985a).

## Lima Beans

Maize, pumpkin and beans is the staple diet in Transkei, the area of highest incidence in Africa.

beans and pumpkin were both eaten more frequently in the high-risk than in the moderate risk area of Transkei
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Beans and pumpkin were both eaten more frequently in the high-risk than in the moderate risk area of Transkei (van Rensburg 1979b). He found 22% of meals

contained beans in a Transkei area of moderate risk, 28% in a high-risk area.

A strong association was found in my case-control study of 130 pairs ( $P=0.016$ ). All 130 SCO patients consumed beans; 123 controls did (Sammon 1998a).

There are no published studies of beans and their relation to oesophageal cancer in the other endemic areas.

Beans are rich in trypsin inhibitor (Bradbury 1985), and therefore may prolong the mitogenic action of growth factors in the lower oesophagus (Sammon 1998b).

## Pumpkin

Pumpkin is a part of the staple diet in Transkei. Van Rensburg (1979b) found 10% of meals in a moderate-risk area of Transkei contained pumpkin, 18% in a high-risk area.

In a case-control study in Transkei (Sammon 1998a) pumpkin on its own did not achieve a significant association with SCO, but in combination with maize and beans, the association was significant and the Odds Ratio 5.50. Both pumpkin and its seeds have trypsin inhibitor activity (Murray and Christeller 1995; Krishnamoorthi et al 1990), and may act to prolong the mitogenic action of growth factors in the lower oesophagus.

## Opium

There is a strong association of SCO with opium metabolites in urine in the Caspian Littoral of Iran (Joint Iran-International Agency for Research on Cancer Study Group 1977). There is no evidence that this is a risk factor in Africa.

## Discussion

The disappearance of alcohol from the risk factors in 'endemic' areas may provide a major clue to the aetiology of endemic SCO. Certainly any theory of aetiology needs to accommodate the fact that alcohol, the greatest risk factor in other areas, becomes insignificant in very high risk areas.

Vitamins and mineral supplements have usually been given in multiples, making it difficult to isolate factors that may be aetiological in deficiency, and protective when adequate. The few that pass the tests of proven deficiency in endemic areas - significantly lower levels in SCO victims, and significant improvement on supplement - are riboflavin and selenium. The evidence for riboflavin is weakened by the results of the Linxian Nutrition Intervention Trial. Lower level evidence exists against vitamin E and beta-carotene deficiency.

Both the Nutrition Intervention Trial and the Dysplasia Trial were of sufficient power to detect small-percentage reductions in incidence of oesophageal cancer. Their failure to detect a significant reduction indicates either that microdeficiencies are not central to the aetiology of endemic oesophageal cancer, or that the initial stages of a successful carcinogenesis happen outwith the six year time-scale of the two intervention trials.

*Solanum nigrum* and lima beans both have inadequate evidence against them to date - one case-control trial only, but both have the possibility of being major aetiological factors since they have highly significant associations in a closely controlled study. Pumpkin also has scanty evidence against it except as part of the Transkei diet of maize, pumpkin and beans, but a genuine association may be present.

The protective value of dietary fat is quite strongly supported by two case-control studies in very high risk areas.

Fresh fruit and vegetables as protective agents have a good case for them worldwide, but inconsistent evidence in high-risk areas. It is possible that the low fruit and vegetable diet is a marker of general dietary deficiency, within which specific factors are important.

## Conclusion

The best-evidenced deficiency associations of SCO are selenium and dietary fat. Riboflavin, vitamin E and beta-carotene may be significant.

*Solanum nigrum*, beans and pumpkin have highly significant evidence as positive associations with SCO, but these are single-study findings.



# 11 Carcinogens

## Chapter summary

No single potent carcinogen has been found on which the endemic incidence of SCO can be blamed. There is good evidence that no such undiscovered potent carcinogen exists. Tobacco is an important carcinogen in Africa with a dose and time-related effect. In the absence of tobacco there would still be a very high incidence of SCO in endemic areas. Human papillomavirus is associated in a minority of cancers, and this may be a causal association. Nitrosamines are found in the environment but not at such a level that they could explain the very high incidences found. Plant mycotoxins are present in the environment and the evidence would support a minor role in the carcinogenic process: fumonisin B1 is not a proven carcinogen for the human oesophagus in the amounts so far demonstrated in Africa.

The pattern of genetic damage in endemic areas is different from those in areas where the disease is more sporadic.

## Chapter content

### Introduction

### Tobacco

### HPV

### Nitrosamines

### Fungi and fungal toxins

### Other substances

### Genetic studies and carcinogens

### Discussion

### Conclusion

### Introduction

There has been a continuous search for one carcinogen on which SCO can be blamed. The search for this single very potent carcinogen has been unsuccessful so far.

### Tobacco

In the Chapter 2 evidence was provided that there is an established strong association with smoking; there is a linear dose-related effect; the relative risk for smokers is

somewhere between 3 and 5; this association is proven in areas of low and of moderate incidence.

There is a consistent association also in studies, of tobacco and SCO in high risk and endemic areas of China. In a nested case-control study within the Linxian Nutrition Intervention Trial, Guo et al (1994) reported a significant risk for tobacco smokers, particularly for long-term smokers.

In Iran, chewing of tobacco (*nass*) is found only in high incidence areas (Joint Iran-International Agency for Research on Cancer Study Group 1977) but there has been no study showing a strong association with SCO. Cook-Mozaffari et al (1979) found no association with *nass* in their case-control study.

In African very high incidence areas case-control studies have all found an association with smoking (Segal et al 1988; Pacella-Norman et al 2002; van Rensburg et al 1985; Parkin et al 1994, Sammon 1992). The relative risk was 2.6 in very high incidence areas of South Africa (van Rensburg et al 1985; Sammon 1992).

Tobacco is clearly a significant factor in SCO in Africa. Two important facts need to be taken account of:

- 1 There is a significant non-smoking minority amongst SCO victims, of between 20 and 30% (Parkin et al 1994; Sammon 1992; van Rensburg et al 1985a; Ahmed 1966). Lack of an accurate smoking prevalence means an estimate of SCO in non-smokers can give little more than just an order of magnitude: if the prevalence of smoking is taken as 53% in the general population, and 72% in SCO patients, with a relative risk of 2.6 for smokers (figures from Sammon 1992) then a population incidence of 100 per 100,000 computes into an incidence in non-smokers of 54/100,000.

- 2 Tobacco usage by SCO victims is relatively low.

This is borne out by Segal et al's study (1988) which showed that patients smoked on average less than 9 cigarettes per day and controls less than 5 per day. In van Rensburg et al's study (1985a), 66% smoked less than 6g of tobacco per day in commercial cigarettes, and 81% smoked less than 6g in hand-rolled cigarettes per day (taking 1 cigarette as equivalent to 1 gram of tobacco).

Tobacco is an active carcinogen in endemic areas. It has a very high cancer-per-gram rate in endemic areas yet its relative risk there (2.6 Sammon 1992; 2.6 van Rensburg et al 1985a; 5.6 Parkin et al 1994) is not higher than other low and medium risk areas where it is between 3 and 5.

## HPV

Human papillomavirus does not have a significant association with SCO in UK (Morgan et al 1997), Japan (Mizobuchi et al 1997), France (Benamouzig et al 1995), Netherlands (Smits et al 1995), or Belgium (Lambot et al 2002).

In Mexico 15 of 17 cancers had positive HPV DNA (Acevedo-Nuno 2004).

In Sichuan, China HPV DNA was positive in 32 out of 152 SCOs (He et al 1997).

Lu et al (1995) examined tissue from 35 SCOs from patients in Linxian, and found no HPV DNA types 16 or 18 in any. From high incidence areas in China 64% of 48 SCOs had positive HPV DNA (Zhou et al 2003). 31 of 48 had HPV 16 DNA.

Chang et al (1990) reported a series of 80 patients with oesophageal dysplasia from Linxian. 66% were HPV DNA positive. A later paper from the same institute (Chang et al 2000) reported on 700 oesophageal cancer specimens from Northern China.

16.9% had HPV DNA present. High risk types HPV 16 and 18 were present in 4.6%. This, by far the largest series, is likely to offer the most accurate picture in the endemic area of China.

A more recent study by Gao et al (2006) confirms a prevalence of 13% of HPV in oesophageal balloon biopsies of asymptomatic adults, but 7% of

16.9% had HPV DNA present. High-risk types HPV 16 and 18 were present in 4.6%. This, by far the largest series, is likely to offer the most accurate picture in the endemic area of China

those with dysplasia, and none of four with SCO tested positive for HPV. This study is too small to negate the evidence of Chang et al's study (2000) that HPV may be significant in a minority of cases of SCO in the endemic area of China.

In Iran 14 of 38 SCO resection samples and 5 of 38 control oesophageal biopsies were positive for HPV DNA. 8 of the 14 positive SCO tumours were positive for HPV 16 or 18 (Farhadi et al 2005).

In South Africa Hille et al (1986) demonstrated HPV antigens in 10% of 70 SCO specimens.

71% of 14 COs were positive for HPV DNA in a study from Cape Town; 15% were positive in benign oesophageal biopsies (Williamson et al 1991).

In Transkei 23 of 50 SCO tissue samples had HPV DNA. Two of the positives were HPV16. Low risk HPV, types 11 and 17, predominated (Matsha et al 2002).

Sitas et al (2007) found a significant association between HPV16 positivity and oesophageal cancer in Johannesburg. The odds ratio for a high antibody level was 1.6.

The evidence allows that HPV may be involved in the aetiology of SCO in a minority of cases.

## Nitrosamines

Nitrosamines are known to have carcinogenic potential, and this is both dose and time related (Lijinsky and Taylor 1978; Lijinsky et al 1981; Sallet et al 2000). Nitrosamines are part of the carcinogen content of tobacco. They can also be found in foods throughout the world for instance in beer (21.3ppb)(Klein et al 1980), in fried bacon (139ppb), and in dried spices (up to 2000ppb)(Havery et al 1976). The lowest level in rats which elicited a carcinogenic response was 132 ppb for over 900 days (Crampton 1980).

Ji and Li (1991) found 1.7ppb NMBA and 1.9ppb NDEA in pickled vegetables in Linxian. More nitrosamines were found in food in Linxian than in a lower incidence area (The Coordinating Group for Research on Etiology of Esophageal Cancer in North China. 1975).

Fasting gastric juice examined in high and low incidence areas for CO demonstrated a positive association between CO risk and gastric nitrosamine (Yang 1992).

Lu et al (1986) found higher levels of urinary excretion of nitrosamines in Linxian, (high incidence area) than in Fanxian (lower incidence area).

Lu SX (1988), in Linxian, found higher levels of nitrosamines in gastric juice from patients with marked oesophageal dysplasia or with cancer than in those with normal epithelium. The mean level of NMBA in gastric juice was 17.09ppb, and the mean level of NDEA was 6.95ppb.

In another study in Linxian, no strong correlation was found between nitrosamine levels and CO (Singer et al 1986).

Nitrosamine levels of food in Iran are low (Kmet et al; Joint Iran International Agency for Research on Cancer Study Group 1977).

Nunn and Nunn (1979) found low levels of volatile nitrosamines in food samples examined in Transkei (a trace, up to 3.2 ppb). Half the samples examined contained nitrosamines. There was a smaller proportion in one lower incidence area than in the higher incidence areas.

93% of samples of imported maize assayed in Netherlands tested positive for Fumonisin B1
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### Fungi and fungal Toxins

Fungal mycotoxins are common wherever maize is used. Fumonisin B1 is a product of *Fusarium verticillioides* (*F. moniliforme*) and is found in commercial corn throughout the world (Marasas 1995). 93% of samples of imported maize assayed in Netherlands tested positive for Fumonisin B1 (de Nijs et al 1998); Mexican children consume 0.9 micrograms of fumonisin per kg per day (Solovey et al 1999).

*F. moniliforme* fed in very large amount to rats over a long time resulted in a considerable yield of liver cancers; but in the oesophagus only some basal cell hyperplasia (Marasas et al 1984).

Fumonisin B1 has carcinogenic properties; fumonisin B1 in high dose intravenously stimulated oesophageal cell proliferation in the rat (Lim et al 1996). Gelderblom et al (1991) gave high dose FB1 to rats for over two years and found a significant incidence of liver tumours; no tumours were found in the oesophagus.

Casteel et al (1993) gave weanling pigs long-term high-dose fumonisin B1. They developed severe liver damage, and papillary downgrowths in the distal oesophageal mucosa. Myburg et al (2002) demonstrated a cytotoxic effect on a human oesophageal cell line when fumonisin B1 was used in combination with a nitrosamine and catechol. Wild et al (1997) did not find any synergistic action of fumonisin B1 and NMBA on the rat oesophagus. Tolleson et al (1996) found fumonisin B1 to be apoptotic and antiproliferative on human oesophageal cells.

Chu and Li (1994) found fumonisin B1 in mouldy corn at levels of up to 155ppm in mouldy maize in Cixian and Linxian. Fumonisin contamination of maize in Linxian was 48% and in low incidence Shangqiu was 25%. In Linxian levels ranged from 1280 to 11300 micrograms/gram (Yoshizawa et al 1994). Wang et al (2000) examined maize from Cixian county - a high risk area for SCO. They found high levels of FB1 in mouldy samples of maize, and low levels in apparently health maize. The frequency of FB1 contamination in the high risk area was twice that in low risk areas, and the quantity of contamination three times higher in the high risk area.

FB1 levels were significantly higher in maize from high incidence areas (average 3.18 mg/kg) of Iran than in samples from a low incidence area (average 0.22 mg/kg) (Shephard et al 2002).

In KwaZulu, South Africa, 33% of rural maize samples contained fumonisin B1, and 33% of volunteers had faecal FB1. In town 6% of maize had FB1 and 6% of people had faecal FB1 (Chelule et al 2001).

Higher levels of *F. verticillioides* were detected in home-grown maize in cytologically abnormal households in high incidence areas of Transkei than in low incidence areas (Marasas et al 1988).

Serum sphingolipids have been proposed as biomarkers of fumonisin exposure. Abnet et al (2001) carried out a case-control study of oesophageal cancer patients. No association was found with serum sphingolipids.

fumonisin levels in human hair in Transkei were found to be higher in the low incidence area of Bizana, than in high incidence Butterworth
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Fumonisin levels in human hair in Transkei were found to be higher in the low incidence area of Bizana, than in high incidence Butterworth (Sewram et al 2003).

### **Other substances**

Opium, a possible mutagen in Iran (Ghadirian et al 1988), has no relevance in Africa.

*Solanum nigrum*, mentioned in detail in chapter 10, may contain carcinogenic substances.

*Mate* drinking in Uruguay has a significant association with SCO (Sewram et al 2003). *Mate* is made from the leaves of the tree *Ilex paraguarensis*. There is no apparent relevance to SCO in Africa

### **Genetic studies and carcinogens**

Present estimates are that six or seven genetic mutations are required to create a gastrointestinal cancer (Uys and van Helden 2003; Gatenby and Gillies 2008). These changes are expressed in capability terms rather than genetic terms and these two can only be occasionally brought together – eg p53 damage affects the ability of a cell to repair itself or undergo apoptosis when a major gene mutation has occurred.

In low to medium incidence areas the prevalence of p53 mutation is relatively high, usually 60-80% of SCOs (Volant et al 1995; Mandard et al 1997; Wang et al 1998; Gaur et al 1997; Tanaka et al 1999). In France 14 of 20 SCOs were positive for p53 mutation (Volant et al 1995). Mandard et al (1997) found 8 of 11 positive.

In Taiwan Wang et al (1998) found 74.6% positive.

Matsha et al (2007) in Cape Town found 70% of 114 SCO patients had p53 damage. There was no correlation between HPV DNA changes and p53 mutations in SCO patients. There was however a significant association between HPV DNA and p73 expression.

A high p53 mutation rate is associated with smoking (Montesano 1997; Franceschi et al 1995; Saeki et al 2002; Yoshikawa et al 2005). Saeki et al (2002) found p53 accumulation in 6 of 7 SCOs where there was a history of heavy drinking and smoking, but in only one of 6 without such a history.

There is a lower level of p53 damage in high incidence areas:

In Linxian, Liang et al (1995) found p53 damage in 5 of 9 SCO patients. In Linxian, Gao et al (1994) found p53 mutations in 16 of 29 samples (55%).

there is a lower level of p53 damage in high incidence areas

In Iran 50% of SCO patients had p53 damage (Sepehr et al 2001).

In Durban, serving a higher incidence area within South Africa 42% were p53 positive (Chetty and Simelane 1999). In Transkei, Gamieldien et al (1998) found p53 damage in 17% of 76 SCOs.

The lower level of p53 mutation in very high incidence areas suggests a different aetiological chain of events from low to medium incidence areas.

## Discussion

Tobacco has a large yield of tumours in endemic areas for a small dose, as compared to for instance the UK where 65% of men smoked cigarettes in 1948, and averaged over 10 per day per male member of the population and the risk of oesophageal cancer was low. The Relative Risk is lower in endemic areas than for (heavier) smokers in the rest of the world. In addition to that the amount of p53 damage is less in endemic areas. Tobacco does have an important role in carcinogenesis in endemic areas but may be responsible for fewer of the steps of oesophageal carcinogenesis. A very high incidence rate for SCO in non-smokers of around 54/100,000 in Transkei confirms that there is a major carcinogenic process at work which is not tobacco-dependent.

HPV is an established carcinogen with much evidence to associate it with oesophageal cancer in the endemic areas of the world. The evidence of percentage involvement in SCO is inconsistent, but the largest series in China suggests a possible involvement of between 5% (Types 16 and 18 present) and 17% (any of the tested types present). There is no adequately powered study from Transkei, but the equivalent from Matsha et al's study would be between 4% and 46%.

Nitrosamines are present in the endemic areas, as elsewhere in the world. The evidence is of a consistent but low level of nitrosamines in China and in Transkei. The levels are not of a sufficiently different order to explain the great differences in incidence, but as known carcinogens they may contribute in some way. This is a moderately researched subject, with low-level and inconsistent evidence.

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although fumonisins are the textbook favourite carcinogen for endemic oesophageal cancer, they do not have a reliable pedigree as oesophageal carcinogens

favourite carcinogen for endemic oesophageal cancer, they do not have a reliable pedigree as oesophageal carcinogens. There is evidence of greater fumonisin B1 in higher incidence areas, but objective measures of fumonisin exposure do not confirm an association.

## Conclusion

Tobacco is a carcinogen in the African situation. Other carcinogens are present, and may have some role in carcinogenesis, but neither a predominant nor an exclusive role.

## 12 Reflux

### Chapter summary

Duodenal fluid reflux into the oesophagus is carcinogenic. Duodenal reflux without gastric content is significantly more powerfully carcinogenic. The evidence supports gastric acid as being a protective factor. In humans, conditions which are associated with reflux and acid suppression, including pernicious anaemia, gastrectomy, and alcohol consumption, are also associated with squamous carcinoma.

### Chapter content

#### Duodenal reflux is carcinogenic

#### Duodenal reflux without gastric content is more carcinogenic

#### Human Evidence

#### Self-induced vomiting

#### Discussion

#### Conclusion

#### Duodenal reflux is carcinogenic

The associations between gastro-oesophageal reflux and Barrett's oesophagus, and between Barrett's oesophagus and adenocarcinoma of the oesophagus are well accepted (Lieberman et al 1997; Conio et al 2002; Shaheen et al 2002). Where the reflux contains duodenal fluid the risk is much higher:

Yamashita et al (1998) working with rats treated with a carcinogen, concluded that pancreatic juice is the most potent oesophageal carcinogen.

With a low dose carcinogen, CO only developed if there was duodenal fluid reflux: then there were similar numbers of SCO and adenocarcinoma (Pera et al 1993).

Miwa showed that refluxed duodenal content <i>per se</i> is carcinogenic
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Miwa showed that refluxed duodenal content *per se* is carcinogenic. In rats without any carcinogen, 83% with duodenogastro-

oesophageal reflux developed CO, mostly adenocarcinoma (Miwa et al 1996).

With reflux of duodenal contents, without gastrectomy (and no carcinogen) all rats had CO at 60 weeks; 40% were SCC, 20% were adenocarcinoma, 40% were adenosquamous (Chen et al 2007). Melo et al (1999) Found that gastro-oesophageal reflux with or without diethylnitrosamine gave rise to oesophageal papillomatosis. Duodenogastro-oesophageal reflux on its own resulted in Barrett's oesophagus in 16.7%, and adenocarcinoma in 16.7%. Duodenogastro-oesophageal reflux plus diethylnitrosamine resulted in 70.6% SCO and 5.9% adenocarcinoma.

## Duodenal reflux without gastric content is more carcinogenic

The picture is significantly different if there is no gastric content. Carcinogenesis with MNAN plus gastrectomy plus oesophageal reflux resulted in 100% induction of squamous carcinoma in 8 rats (Seto et al 1991).

Ireland et al (1996) operated on groups of rats to produce duodenal reflux into the oesophagus with variable amounts of accompanying gastric fluid reflux. All were given MNAN. There was a progressive increase in prevalence of carcinoma as less gastric juice refluxed with the duodenal juice. The total tumours were 184 adenocarcinomas and 139 squamous carcinomas.

there was a progressive increase in prevalence of carcinoma as less gastric juice refluxed with the duodenal juice
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oesophagus with variable amounts of accompanying gastric fluid reflux. All were given MNAN. There was a progressive increase in prevalence of carcinoma as less gastric juice refluxed with the duodenal juice. The total tumours were 184 adenocarcinomas and 139

Aoyagi et al (1999) found that alkaline (duodenal) regurgitation into the oesophagus in gastrectomised rats without carcinogen resulted in SCO of the oesophagus in rats by 50 weeks.

It is not completely clear from these studies whether it is simply the lack of acid which is the factor that increases the risk that duodenal reflux creates, or whether there is some other factor involved.

A highly relevant study is that by Clark et al (1994) which has some similarities to the situation in Africa: reflux of gastroduodenal juice and the administration of an oesophageal carcinogen had their greatest yield of cancers when the rats were fed on a high corn (maize) oil diet: 60% of these cancers were squamous. Clark et al did not measure acidity, but studies by Schepp et al (1988) make it clear that rats on a high corn oil diet would have had a significant depression of gastric acidity (see chapter 9). This suggests that it is the acid which is protective, and a lack of acid is promotive of oesophageal cancer when there is duodeno-oesophageal reflux.

## Human evidence

Patients with oesophageal cancer in China had lower oesophageal pressure and pathological gastro-oesophageal reflux (Wang 1993). It is not possible to know whether this was a problem that predated carcinogenesis in individuals.

Galli et al (2002) found pathological reflux in 81% of patients with squamous cancer of the larynx or hypolarynx, closely related tumours.

## Self-induced vomiting

Vomiting is seen as a way of 'cleansing' from physical or spiritual problems, and is widely practised in South Africa. 91% of SCO victims in Transkei and 85% of controls practised self-induced vomiting (Sammon 1992). Only a third of those used traditional medicines to induce vomiting, the remainder using salt, or not needing anything to initiate regurgitation. Three-quarters of those who vomit in this way regurgitate bile. In this study there was no association between SCO and self-induced vomiting.

Matsha et al (2006a) carried out brush cytological oesophageal biopsy on 478 self-referred patients in Transkei. They found that 80.5% of males and 79.1% of females practised self-induced vomiting, and that there was a significant association between self-induced vomiting and chronic oesophageal inflammation. There is no direct link



to SCO since chronic inflammation of the oesophagus has not been demonstrated as a precursor lesion for SCO (Wang et al 2005).

it is possible that self-induced vomiting is a symptom rather than a cause of disease
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In Transkei, a large majority of the population have significant heartburn (Sammon 1994), and it is possible that the wish to and almost universal ability to carry out self-induced vomiting is an indicator of abnormal lower oesophageal sphincter laxity; that self-induced vomiting is a symptom rather than a cause of disease.

## Discussion

Experimental animal evidence shows that reflux predisposes to carcinogenesis; and without carcinogen is more slowly carcinogenic. If there is no gastric acid content, the rate of cancer production is higher, and many of the cancers are squamous. GI content from beyond the duodenum is particularly aggressive.

In humans, conditions which are associated with reflux and acid suppression including gastrectomy, alcohol consumption and pernicious anaemia are also associated with squamous carcinoma. There is a *prima facie* case that the reflux is a factor or the factor which is responsible.

## Conclusion

Duodenal fluid reflux into the oesophagus is carcinogenic. Duodenal reflux without gastric content is significantly more powerfully carcinogenic. The evidence supports gastric acid as being the protective factor. In humans, conditions which are associated with reflux and acid suppression are also associated with squamous carcinoma.

## **13 What causes oesophageal cancer?**

### **Chapter summary**

High level and consistent evidence exists to associate SCO with maize as the monostaple, the diet of maize pumpkin and beans, maize meal consumption, tobacco, and low dietary fat intake. Lower level but consistent evidence supports a link with human papillomavirus, and deficiencies of vitamin and selenium intake. Pumpkin, beans and *Solanum nigrum* have high-level but inadequately corroborated evidence implicating them. Other agents including fumonisins, nitrosamines, traditional beer and alcohol have had adequate research and have no convincing evidence against them.

The evidence points to diet as the base for endemic incidences of the disease. A high maize meal intake, poverty of dietary fat and dietary deficiencies including selenium are the best evidenced associations.

The history of the availability of commercially milled maize and the time-scale of the 'epidemic' are compatible with a causal association.

### **Chapter content**

#### **Introduction**

#### **The endemic base**

#### **Past and present theories of causation**

#### **Assessment of possible aetiological factors**

#### **Discussion**

#### **Conclusion**

#### **Introduction**

Current evidence suggests that there is a progressive overcoming of perhaps seven barriers as an active and growing cancer evolves. We do not yet have enough information to identify which agent alone, or which agents in combination can cause any one of these seven successful evolutions, therefore the models of sequential and distinct predisposition or initiation by one agent and promotion by another are unhelpful, and may be inaccurate.

At this stage in our knowledge it is more helpful to attempt to identify some or all of the agents which are additive or synergistic in influencing the genetic evolution of cells which are functionally malignant.

Definition of the precise molecular mechanism of production of SCO in the endemic regions is an important objective. There may not yet be adequate information to achieve this, but this does not mean that we cannot identify the gross cause(s) of the disease, and therefore alter circumstances to reduce the incidence.

## The endemic base

Something - a single agent, or more than one agent or circumstance is responsible for the very high incidence of SCO in certain parts of Africa. This may in theory be a different agent, different agents, or different combinations of agents in each place.

## Past and present theories of causation for endemic areas of Africa

Published theories belong to one of two major views:-

- 1 The BIG carcinogen
- 2 Nutritional disposition and ordinary carcinogens

### 1 The BIG carcinogen

'The epidemic-like increase to high rates of oesophageal cancer in the Transkei over the past 36 years suggests the introduction of a strong carcinogen into the environment. The marked and constant gradient of incidence, from low incidence in the Northeast to high incidence in the Southwest should have facilitated the search for such a carcinogen. In fact the search has been singularly disappointing, although carcinogens have been found in unspectacular amounts' (Rose 1978).

To this general category of 'the big carcinogen' belong:

Ilicit alcoholic brews (Burrell 1957). Burrell mentioned carbide, metal polish, methyl alcohol and acetylene as among contents of these drinks in South Africa.

Fumonisin – the current textbook answer.

An unidentified carcinogen in the full Transkei diet (Purchase et al 1975)

Fusarium (Jaskiewicz et al 1987; Craddock 1987; Isaacson 2005)

Carcinogens in maize beer (Bradshaw, McGlashan and Harington 1983)

Fusarin C (Lu et al 1991)

Nitrosamines (Mirvish et al 1993; Du Plessis et al 1969)

*Alternaria alternata* (Liu et al 1992)

HPV (Morris and Price 1987; Hille et al 1986; Williamson et al 1991)

*Bidens Pilosa* (Mirvish et al 1985)

### 2 Nutritional predisposition and ordinary carcinogens

Van Rensburg (1981) noted the strong relationship between corn and wheat and CO. 'without a single exception, all of the many communities found to be living mostly on wheat or corn had a considerable oesophageal cancer risk'. He agreed the possibility of the single carcinogen '..either there is, on a universal basis, a unique carcinogen peculiar to wheat and corn....', but proceeded to the other option – 'or commonly occurring carcinogens (e.g. polycyclic aromatic hydrocarbons, nitrosamines in food and drink, and tobacco smoke carcinogens) are, at the levels to which most people are exposed, collectively adequate to induce transformation in the nutritionally disposed esophageal epithelial tissue, resulting in moderately high cancer rates'.

Rose (1979) wrote of 'increasing susceptibility, through lack of protective foods, to carcinogens already present in the environment.....a multifactorial situation.....an imbalance between those factors which protect and those which cause insult to the epithelium of the oesophagus'.

Warwick and Harington (1975) blamed 'a sustained alkaline irrigation of complex promoting and/or carcinogenic substances. These effects could be modified or prompted by antecedent pathology such as oesophagitis, pellagrous lesions, the

excessive consumption of alcohol, and the persistent use of emetics derived mainly from plants..’.

### Assessment of possible aetiological factors

There are no cohort studies available for SCO in Africa.

**Best evidence of Associations in high-risk areas (Brackets indicate a contrary or negative finding)**

Factor	Close CCS in a high-incidence area	CCS	Patient study	Population study	Environmental study	Animal study
Maize as monostaple			AMS*1992 SJvR1985a	SJvR1981 PC 1971		IHFP1975
Maize pumpkin and beans	AMS1998a					SJvR1974
Maize meal	SJvR1985a					SJvR1985
Beans	AMS1992					IHFP1975
Tobacco	AMS1992 SJvR1985a	IS1988 RP-N2002 DMP1994 WG1994		(HH1975) (YY1993) GDT2005		
Alcohol	(SJvR1985a)	RP-N2002 (DMP1994)		(HH1975) (YY1993)		
Traditional beer	(AMS1992) (SJvR1985)	IS1988	(TM2006b)			
Wild vegetables						IHFP1975 SJvR1974
Other dietary fat protective	SJvR1985a AMS1992					
<i>Solanum nigrum</i>	AMS1992					IHFP1975
Fruit protective	(SJvR1985a) PJCM1979	(JYL1989)		KJ1989 HH1975 GDT2005		
Green vegetables protective	(SJvR1985a) PJCM1979	WG1994 (JYL1989)		KJ1989 HH1975		
Riboflavin			(NM1985) NM1987	SJvR1983; JHJ1952; GG1981 HH1975		FH1984
Nicotinic acid deficiency				SJvR1983; JHJ1952; GG1981		
Vitamin E deficiency			KJ1988 PRT1994	KJ1988 PDvH1987		

<b>Folic acid</b>			KJ1988	KJ1989 PDvH1987		
<b>Vitamin A deficiency</b>			KJ1988 (NM1985) NM1987	KJ1989 PDvH1987 HH1975		
<b>Zinc deficiency</b>			(NM1985) NM1987 (JK1989)	SJvR1983	RJWB1966 MCL1979	LYF1997
<b>Magnesium deficiency</b>				SJvR1983	MCL1979	
<b>Molybdenum deficiency</b>					RJWB1966	
<b>Selenium deficiency</b>			KJ1988 KJ1989 WJL1991 PRT1994	(MN2004)		JDB1986
<b>Human papillomavirus</b>			TM2002 ALW1991 JJH1986 MJH1989 (SL1995) FS2007 (GFG2006) FC2000 FC1990			
<b>Fumonisin</b>	(CCA2001)			(VS 2003)	GSS 2002 HW2000 TY1994	RBM 2000 (WCG199)
<b>Nitrosamines</b>			SHL1987 SXL1988	SHL1986 WXY1992	(MCL1979) JIA 1977 (HH1975)	DS1976
<b>Fungal contamination</b>				WFOM1988		

\* although this was a case-control study, the evidence about maize was not case-controlled.

## Discussion

### Maize

The evidence is compelling. The disease in Africa only occurs at a high incidence in communities where maize is the staple. In close case-control studies, all SCO victims consume maize. The association is too strongly and too consistently proven for it to be spurious: either maize itself is a problem or there is a consistent problem contaminant.

Some feature of the maize diet is causative: without maize there is no high incidence area in Africa. Maize is an essential of the endemic situation in Africa.

### Pumpkin and beans

The evidence for pumpkin is at best moderate. There is a high relative risk in one case-control study for a diet of maize, pumpkin and beans (5.5). For beans the

evidence is stronger: all 130 of a series of oesophageal cancer patients in Transkei consumed beans. This was significant ( $P=0.016$ ) and the odds ratio not calculable because all cases ate beans. There is the possibility of a spurious association.

The full Transkei diet of maize, beans and two wild vegetables caused epithelial cell dysplasia of the oesophagus in rats. In a study of diet and intragastric pH in rural Transkeians, pumpkin and beans together had the effect of raising the pH independent of maize consumption. If pH change in the stomach is a part of the aetiological process, then the association with pumpkin and beans is almost certainly genuine.

### **Maize meal**

The association with maize in the form of maize meal is a robust association. It has been reported in a community which has maize as its staple, and in which it is assumed that all people use maize. It is dose-related and carries a high relative risk. The relative risk results have been mirrored in two studies in Italy - a different continent and a different culture. There is a credible mechanism to link maize meal and SCO. Could this association be spurious? Van Renburg et al (1985a) and Rose (1975) wrote of SCO victims as coming from a section of the community which is in a transitional state of westernisation – a rural base and at least some cash income. This section of the community may have other peculiar attributes which cause the disease; but those who are in a transient state of westernisation are throwing off rather than acquiring exotic eating or social habits. Furthermore, after half a century of looking, no such other risk factor has come to light.

There may be a potent and as yet undiscovered carcinogenic contaminant which is found only in maize meal. This has to have a very low probability in view of the amount of research that has gone into this subject over many decades.

Maize meal is an agent which has been shown in multiple case-control studies, in different continents, to have a higher relative risk than the two accepted causative agents smoking and alcohol; an agent which has a dose-related effect; an agent which was rapidly made available to the mass of rural people just before the ‘epidemic’ began. There is no other

without maize meal, historically and by case-control study, there is no high incidence of SCO
---

reasonable conclusion than that within communities where

maize is the staple, maize meal is a major aetiological agent for SCO. Without maize meal, historically and by case-control study, there is no high incidence of SCO. Maize meal is an essential part of the endemic factor.

### **Tobacco**

Tobacco is a causal agent in endemic areas. Tobacco smoking in Transkei has a RR of 2.64 (Sammon 1992). In Natal Zulus, it was 2.64 (van Rensburg et al 1985a). The evidence is consistent and reliable worldwide as well as in endemic areas of Africa. It is not however a sufficient cause in itself for the high incidence. Non-smokers in Transkei (Sammon 1992) account for 28% of SCO victims. The incidence rate for non-smokers in Transkei is such that the disease must still be considered as endemic for non-smokers. Tobacco is important in endemic areas of Africa, but cannot be part of the endemic factor. It is of interest that tobacco is not a proven major factor in either of the other high risk areas – the Caspian Littoral and Linxian.

### **Alcohol**

Alcohol has a clear and dose-related association with SCO throughout the world except for high-risk areas, where there is no association. Possible reasons for this are discussed in the chapter 10.

### **Traditional beer**

Traditional beer consumption is a strong marker of that section of the population which is susceptible to SCO, but the association disappears in close case-control studies.

### **Other dietary fat**

This is another well-evidenced association, with bought fat (butter, margarine, cooking oil) coming up as a strong negative association in two close case-controlled studies. In van Rensburg et al's study (1985a) there was a strong protective effect of butter and margarine; in my own study (Sammon 1992) a protective effect of bought fat. It is possible that it is spurious, and that a low level of buying of fat is a marker of

a negative strong association in two close case-controlled studies
--

the subset of the community which is particularly susceptible to SCO, however there is evidence that the

amount of fat in the diet in Transkei has a direct effect on the upper GI tract: low levels of fat in the diet are associated with a high salivary PGE2 (Sammon and Morgan 2002).

### **Fruit and green vegetables**

Fruit and green vegetables are associated worldwide with a reduction in oesophageal cancer, and specifically squamous cancer. There is no strong evidence for this in endemic areas of Africa. Van Rensburg found no significant effect in his case-control study of Zulus. There is however an association of mild oesophageal dysplasia with a low intake of green vegetables and fruit in a high risk area (Jaskiewicz et al 1990). In the Caspian Littoral of Iran, Cook-Mozaffari et al (1979) did find a protective effect of both fruit and vegetables. The evidence is equivocal from Linxian (Guo et al 1994; Li et al 1989).

### ***Solanum nigrum***

The single finding of an association between SCO and *Solanum nigrum* in a closely controlled case-control study (Sammon 1992) may be spurious. In favour of the association being genuine are two pieces of evidence: the relative risk was higher than that for tobacco; and *S nigrum* is part of the 'full Transkei diet' of maize, beans, *Solanum nigrum* and *Sonchus oleraceus* which caused oesophageal epithelial dysplasia in Purchase et al's experiments on rats (Purchase et al 1975). In addition it has proven effects on the upper GI tract of reduction of acid production.

### **Deficiencies**

Deficiencies of riboflavin, nicotinic acid, vitamin E, folic acid, vitamin A, zinc, magnesium, molybdenum and selenium all have population associations with SCO. There are associations with dysplasia patients for deficiencies of vitamins A, E, B12 and folate. The evidence for selenium deficiency involvement is consistent, with four studies linking low selenium levels with either dysplasia or with SCO.

### **HPV**

There are consistent findings of associations of SCO with HPV, and good reasons to believe the association may be causal. The association applies to a minority of patients only and means that, as with tobacco, HPV cannot be a part of the endemic base.

### **Fumonisin and nitrosamines**

Some animal studies have failed to demonstrate a carcinogenic effect on the oesophagus either alone or in combination with a known carcinogen (Gelderblom et al 1991; Wild et al 1997).

Myburg et al (2002) found a low cytotoxic effect of Fumonisin B1 alone on a human oesophageal cell line, but a greater cytotoxicity in combination with DEN, a known oesophageal carcinogen.

There are more fumonisins in maize in high risk areas; Iran (Shephard et al 2002); Cixian, China (Wang et al 2000; Yoshizawa et al 1994).

There has been only one reported case-control study that looked at the association between fumonisin B1 and SCO; Abnet et al (2001) studied sphingolipids as markers of fumonisin exposure in SCO patients in Linxian, China, and came up with negative result.

In Transkei, Sewram et al (2003) found higher fumonisin B1 levels in the hair of those in the low incidence area of Transkei (Bizana) than in the high incidence area of Butterworth, again casting doubt on whether there is any association.

There is an abundance of evidence about Fumonisin B1, but none positive that brings it any closer to SCO than environmental studies. The two closer patient studies are negative. There is no

there is an abundance of evidence about fumonisin B1, but none positive that brings it any closer to SCO than environmental studies
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evidence that would put fumonisins in the category of endemic base, or part of the endemic base, or even as a major agent in the aetiology of SCO.

Nitrosamines are proven oesophageal carcinogens. In China, urinary metabolites of nitrosamines are higher in the population in Linxian (high risk) than in Fanxian (low risk area for SCO) (Lu SH et al 1986). Yang (1992) had similar findings in different counties of China.

Nitrosamines are low in food in Iran (Kmet 1974). Similarly in Transkei very low levels of nitrosamines were found in food samples tested by Laker (1979), with no consistent correlation with high incidence and low incidence areas. This is a fairly well researched subject, with low-level and inconsistent results. Nitrosamines are present in the environment in endemic areas of Africa, but not at a level which is markedly different from other non-endemic areas. They may form part of the carcinogenic background to oesophageal cancer, but cannot be either the endemic base or a part of it.

### **The endemic base**

Tobacco has compelling evidence that it is a causal agent for SCO in endemic areas. *Solanum nigrum* and human papillomavirus also have significant claims to being aetiological agents in endemic areas. But for each of these, there is a significant number of SCO victims who are known not to be exposed. Furthermore the yield of SCO victims among tobacco users is extraordinarily high.



All the evidence points clearly to diet as containing all the elements of the endemic base. Credible candidates for endemic base are maize as a staple, maize meal, low fat intake, other dietary deficiencies including selenium, and beans. Neither maize as monostaple nor maize meal on its own could be the sole causative agent: maize as monostaple was common in the nineteenth century in Africa, and was accompanied by widespread pellagra, but not by oesophageal cancer; maize meal is heavily used in parts of Northern Italy, and is accompanied by only moderate levels of oesophageal cancer. Maize as monostaple was almost certainly accompanied by a low fat intake and by multiple vitamin and micronutrient deficiencies in the nineteenth century, before the rise of SCO. It is possible that there has been more leaching away of micronutrients from the soil over the last century, but this is unlikely to be of such an

credible candidates for endemic base are maize as a staple, maize meal, low fat intake, other dietary deficiencies including selenium, and beans
--

order of magnitude as to change a negligible incidence of SCO to an endemic incidence. Commercially milled maize meal provides the only certainly new feature of the diet.

If maize meal is an essential part of the endemic base, is a new part of the endemic base, and is not the sole agent of the endemic base, then other components of the diet, new or not, must be parts of the endemic base. Maize as monostaple provides a basis of profound deficiency. Maize meal steadily changes its composition after milling, and is identifiably chemically different from whole-grain maize.

The next candidate with strong evidence is lack of fatty variety in the diet: two case-control studies in very high incidence areas demonstrated this association.

The evidence for an association with beans is from only one study, and is uncertain only because of that – there needs to be further investigation before any worthwhile conclusion may be drawn. There have been many studies of vitamin and mineral deficiencies, with the strongest evidence coming out against deficiency of selenium, and rather patchy evidence against any vitamin deficiencies. Intervention studies involving vitamin and mineral supplements similarly have been inconsistent in their results.

From the point of view of levels of evidence, the prime suspects for forming the endemic base are maize, maize meal, poverty of dietary fat, and a background of general dietary deficiency including selenium. It is possible that there is some other factor which has been missed, or not yet discovered, but it seems wise to consider the strong evidence we have against certain dietary elements, and attempt an understanding of how they may have combined to cause the rise of this disease.

### **An endemic base of maize meal, poverty of dietary fat, and a background of general dietary deficiency including selenium**

How does fit with the facts?

Does this fit with the history of the development of the disease in Africa?

Does this fit with the regional and local distribution of the disease?

Does this fit with the social section of the community who get SCO?

### **History**

Prior to around 1930, maize meal was generally available to the poorer rural population of Africa only in small amounts, nearly all freshly ground at home. From

1930 onwards, and rapidly over the two decades that followed, commercially milled maize meal became freely available, in quantities often of 50kg, to subsistence farmers in rural districts. This was either their own maize milled locally, other locally produced maize milled locally, or milled maize imported from outside the area.

This mass availability of maize meal did occur suddenly in the 1930s and 1940s. It started from almost zero to

this mass availability of maize meal did occur suddenly in the 1930s and 1940s
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becoming the major portion of the diet for large sections of the community. It affected those in rural poverty with a little cash income. It was at first patchily available as local milling became available.

### **Regional and local distribution of SCO**

The introduction of commercial maize in large amounts varied and still varies through Africa. Local milling was introduced early in South Africa and in Kenya. The first small-scale hammer mills to be manufactured in Africa were made in East London, South Africa in 1928.

Were they marketed locally first of all, with a much higher proportion of Southern Transkei having access to milled maize meal in the early days, than the more distant and less accessible Northern Transkei? – That would explain local variations and apparent spread of the disease.

### **Who gets SCO?**

It is the rural poor but not the poorest; people who have a little cash income to buy maize meal. People in a transitional state of westernisation – they are rural poor, have a globally deficient diet, and have abandoned home-grinding of maize in favour of bought maize meal.

It is possible that the distribution of SCO in Africa reflects the use of large-unit commercial maize meal rather than the distribution of maize.

### **Is there a mechanism to explain how maize meal and other dietary deficiencies could cause endemic levels of SCO?**

Yes – see Chapter 14.

## 14 A proposed aetiology of SCO

### Chapter summary

Maize meal, a low-fat diet, and other microdeficiencies including deficiency of selenium, together create an excess production of PGE<sub>2</sub> in the stomach. Excess PGE<sub>2</sub> causes inhibition of gastric acid production, and duodeno-gastro-oesophageal reflux. These physiological abnormalities are carcinogenic.

Each of these steps is evidenced in theory. Each step has good corroborating evidence in high risk and endemic areas of Africa.

This aetiological chain provides an explanation for the high incidence of the disease in certain areas, its timescale, apparent spread, the lack of influence of alcohol in endemic areas, and the targeting of the rural transitional population.

Other factors which boost the incidence of SCO in certain communities and individuals include tobacco, HPV, pumpkin and beans, and may also include *Solanum nigrum*.

### Chapter content

#### General

#### The endemic base

#### Tobacco

#### Boost factors

#### Three levels of aetiological agents

#### Facts that need explained

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#### General

Gatenby and Gillies (2008) state that 6 proliferation barriers require to be overcome by cells that are to become malignant, and describe a process of natural selection of cells as they evolve to overcome the barriers. Multiple genetic mutations are required, and a variety of genetic change may be able to overcome the same proliferation barrier. It is not necessary accurately to fit different agents into the categories of predisposition, initiation, carcinogenesis or promotion in order to know what are or are not aetiological agents and with our present knowledge it is not possible.

Agents that must be fitted into the aetiological pathway are:

- 1 Endemic factors: maize meal, low dietary fat, global dietary deficiencies associated with a maize-based diet including selenium.
- 2 Tobacco

The following agents have a probable but uncertain place

3 Beans, pumpkin, *Solanum nigrum* and HPV

## The Endemic Base

### **Maize meal, low dietary fat, global dietary deficiency including selenium.**

Maize meal degenerates significantly after milling, undergoing de-esterification of linoleic acid, but with relatively little further oxidation of fatty acids. Degenerated maize meal is highly active physiologically in the stomach, but has little associated taste change (rancidity) to warn of that highly active state. Home-ground and immediately used maize meal has the least opportunity to degrade; commercially ground meal, with a milling-to-retail delay, and then a purchase-to-consumption delay has the greatest opportunity to degrade; for purchased maize meal, large quantities bought and used slowly in the home over weeks or even months will suffer maximum degradation.

I have demonstrated that to up to 363 mg of free linoleic acid per 100g maize meal may be available in long-stored maize meal, equivalent to over 1g per day of free linoleic acid in a maize-dependent diet. At three months after milling, and storage in moderate conditions, there is already 122mg per 100grams meal.

Free linoleic acid in the diet has proven effects – it increases the level of arachidonic acid, which in turn increases production of PGE2 within the stomach. Deficiency of other dietary fat preferentially causes production of PGE2. Deficiency of selenium preferentially causes production of PGE2.

Excess production of PGE2 results in reduction of gastric acid production and reduction of the lower oesophageal sphincter tone and the pyloric sphincter tone.

Does this happen? There is strong evidence that it does: in Transkei more than half the population has an intragastric pH of over 4. Much of the population suffers from the heartburn and regurgitation, sometimes of bile, that accompanies a reduction in lower oesophageal sphincter tone. This heartburn and regurgitation is associated with consumption of maize meal products.

Does this cause SCO? It is difficult to see how it could do otherwise. Reflux is a known potent cause of oesophageal cancer, and in the presence of carcinogens, there is a high yield of tumours.

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When there is no acid content, this yield of tumours is principally squamous, and if the reflux includes duodenal fluid, the yield is even greater. In addition, PGE2 itself is mutagenic in the oesophagus.

In summary: in those who have a high daily intake of non-esterified linoleic acid, and poor intake of fat and selenium, there is a chemically induced low-acid duodeno-gastro-oesophageal reflux which is in itself strongly carcinogenic. It is accompanied by a high level of PGE2 which is carcinogenic.

## Tobacco

The addition of known carcinogens such as the nitrosamines of tobacco greatly increases the yield of reflux-induced oesophageal cancers even when the carcinogens are at a relatively low dose. HPV and other carcinogens may also be active.

## **Boost Factors**

Factors that boost oesophageal cancer locally may include the availability and use of *S. nigrum*, consumption of beans and pumpkin. All of these may contribute to SCO prevalence by adding to the effect of the endemic base factors, or by direct carcinogenic action, or by some other mechanism. For instance Transkei, an area of exceptionally high risk, has a high local consumption of *S. nigrum*, pumpkin and beans.

## **Three levels of aetiological agents**

There are therefore three levels of agent:

- 1 The endemic base of maize as monostaple, maize meal, low fat, low vitamins and selenium.
- 2 Known carcinogens: tobacco, HPV and possibly others.
- 3 Local boost factors including *S. nigrum*, beans, pumpkin

## **Facts that need explained**

within an aetiological pathway are:

The timescale

Apparent spread of the disease

The diminishing influence of alcohol as the incidence rises

National regional and local variations in incidence

Susceptibility of the rural intermediate culture group

Gender differences in incidence

### **The timescale**

The rapid rise in disease took place soon after the introduction of rural maize milling, when maize meal in large quantities and often in large packets rapidly became available to the most rural of people.

### **Apparent spread of the disease**

The spread of the disease may be found to mirror the spread of easy availability and use of locally machine-milled and commercial maize meal.

### **The diminishing influence of alcohol as the incidence rises**

The endemic base and alcohol both have the same end-pathway of acid suppression and reflux. They are initially additive. When a maximal suppression of acid and of lower oesophageal sphincter tone is achieved by the endemic base, then there is no further change that alcohol can bring about, and alcohol no longer increases the risk of SCO. This agrees with findings on the effect of alcohol being measureable except in the highest risk communities.

### **National regional and local variations in incidence**

All susceptible African communities have maize as their staple, but have varying habits with respect to the contribution that maize meal makes to diet, and the pattern of purchase and storage of that maize meal. They have varying habits with respect to consumption of other fats, and the availability of micronutrients in their diet. The presence of boost factors varies greatly throughout Africa.

### **Susceptibility of the rural intermediate culture group**

People in a 'transitional' state are those who no longer cling to old ways of preparing food. They are open to buying rather than grinding their own maize meal, and open to a rapid change in diet from whole grain to milled maize as principal component of their diet. They have a little cash income, enough to pay for maize meal, not enough to guarantee variety of diet including adequate bought fat.

### **Gender differences in incidence**

In nearly all communities, men use more tobacco than women. In communities where the effect of the endemic base is great, susceptibility to all potential oesophageal carcinogens rises; HPV and other possible carcinogens, particularly food-associated carcinogens are less gender-specific. As the background risk associated with the endemic base rises, these lower-grade carcinogens take a proportionally greater toll, and the M:F ration comes nearer to unity.

### **Conclusion**

There is a well-evidenced aetiological chain linking local diet to endemic incidence of oesophageal cancer in Africa.

## **15 Preventative actions**

### **Chapter summary**

On the basis of already broadly accepted ideas of causation, health education to ensure a variety of diet and education about the very high danger of tobacco in the endemic situation are all justified, but not likely to be immediately or highly successful. The most logical education message is that added dietary fat is preventative.

Stabilisation treatment of maize meal and strict distribution and storage conditions may be both effective and achievable. Omega 3 fatty acid supplementation of maize meal, if possible in cost and taste terms, is an alternative which would at the same time make a good contribution to general health.

For the generations already long-exposed to the endemic base factors, strict avoidance of carcinogens may be the only preventative option.

### **Chapter contents**

#### **Introduction**

#### **The endemic base**

#### **Carcinogens**

#### **Boost factors**

#### **Discussion**

#### **Conclusion**

#### **Introduction**

The introduction of effective preventative measures requires careful planning with multidisciplinary input. The decisions are as much political as scientific. In this chapter I have attempted only initial and undeveloped thoughts on what might be effective and what might be possible.

#### **The endemic base**

The major problems are:

- Degradation of triglycerides in milled maize meal
- Inadequate dietary fat
- Micronutrient deficiencies

#### **Possible actions**

- Reduce use of bought and stored maize meal

- Health education; poverty alleviation
- Reduce or prevent degradation of triglycerides
  - Subject maize meal to quality restrictions at time of sale, reduced retail unit size, short shelf life
  - Add to maize meal a substance which creates rancidity before significant free linoleic acid is produced
  - Careful moisture control/packaging of marketed maize meal
  - Premarketing heat stabilisation of fatty acids in maize meal
  - Add a lipase inhibitor to all maize meal
- Improve dietary omega 3: omega 6 ratio
  - Health education
  - Fortification of maize meal with an omega 3 fatty acid
- Improve micronutrients in diet
  - Continued fortification of maize meal; but note that on its own this did not reduce the incidence of SCO in the Linxian Nutrition Intervention Trial (Wang et al 1994).

## Carcinogens

- Reduce tobacco usage
  - Health education and control of advertising
  - Taxation
- Reduce exposure to HPV
  - Immunisation programme

## Boost factors

- Reduce use of beans and pumpkin
  - Education (Politically difficult if not impossible)
- Reduce use of *Solanum nigrum*
  - Education

## Actions on theoretical grounds

- Encourage use of local plants with high flavonoid content.
- Encourage use of local plant PG synthesis inhibitors – there are many (Jager et al 1995).

## Discussion

Preventative measures require to be targeted at the susceptible population, effective, affordable, and acceptable to the communities concerned.

Those which depend on health education are also dependent on an effective method of dissemination of the information, and a population willing to listen to and follow health messages. This may apply to some of the affected communities in Africa.

the single most effective measure would be an increase in amount and variety of dietary fat

The option of major dietary change is almost impossible for rural people with little income. The single most effective measure would be an increase in amount and variety of dietary fat. This message would be acceptable in terms of taste, but involves greater food costs.

Treatment and subsequent packaging and marketing of maize meal in such a way that there is zero or minimal degradation of triglycerides at the time of consumption would be the ideal. The addition of an effective and inexpensive lipase inhibitor at milling



could be considered if it did not alter subsequent human digestion. Moisture control and heat treatment may offer partial solutions. The addition of a 'rancidity' agent would be unpopular.

Fortification of maize meal with an omega 3 fatty acid appears to be a good preventative, and has many other good health spin-offs for marginally malnourished communities. Taste and cost require assessment.

There is a generation, or even two generations whose oesophageal mucosae are already severely damaged by the endemic base and amongst whom there will be a continuing harvest of SCO. The measures mentioned above may be inadequate to prevent their disease. Very careful reduction in carcinogen exposure may be the only effective measure for them.

there is a generation, or even two generations whose oesophageal mucosae are already severely damaged

The final reduction to single figures incidences can only be achieved when a balanced diet is achieved even for the poor, and that may be related to per capita income more than to health interventions.

## Conclusion

Preventative strategy needs multidisciplinary and political input. Further micronutrient fortification of maize meal has no evidence base to support it. Avenues to investigate include stabilisation treatment of maize meal followed by careful storage and marketing; omega 3 fatty acid supplementation of maize meal; and appropriate health education – primarily on the value of additional dietary fat.

## **16 Areas for further research**

Consumption of *S nigrum* and SCO in Africa

The oesophageal milieu in Africa

The degeneration of maize meal and how to affect that

History of mechanised milling in Africa and its relationship with the spread of SCO

Different cultures and different uses of maize meal within Africa and its relationship to SCO

Marketed sizes of maize meal packets and SCO prevalence

Close case-controlled studies of maize meal purchase, their pattern of use and SCO

Close case-controlled studies of HPV and SCO.

Identification of a rancidity agent which is taste-neutral until the maize meal is no longer safe.

PGE2 in the stomach and oesophagus in Africa

The dose effect of omega-3 fatty acids in reducing gastric PGE2

Beans and pumpkin and their relationship to SCO

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