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Aetiology of Oesophageal Cancer in Africa - A Review of Historical and Current Evidence

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Abstract

There is no current agreement on the cause of squamous cancer of the oesophagus in Africa, a major cause of morbidity and mortality in East and Southern Africa. The remarkable history is reviewed together with all recent evidence using a literature search.

There are consistent and continuing associations with maize and with tobacco. Changes of type of maize, patterns of consumption and processing occurred around 1930, and a rapid rise of oesophageal cancer dated from that time.

Tobacco has a worldwide association with cancer of the oesophagus, but there is a substantial minority of non-users in high incidence areas. Other carcinogens have come under suspicion, but there is evidence against any of these acting as the principal carcinogenic influence in Africa. Recent studies in Japan and in South Africa have shown an association between non-acid gastro-oesophageal reflux and squamous cancer of the oesophagus.

There is no credible candidate for principal oesophageal carcinogen in Africa. There is good reason to look again at milled maize: its deficiencies, contaminations, and degenerative processes. Associations between diet, non-acid reflux and squamous cancer of the oesophagus merit further study.

Keywords: oesophageal cancer, diet, epidemiology

1. Introduction

Cancer of the oesophagus is a major cause of death in East and Southern Africa. Many substances have been blamed for the high incidence of this disease, but the lack of agreement about aetiology continues to stand in the way of effective preventive measures. This review is intended to assess the evidence available and identify research priorities.

In seeking to understand the enigma of the very high incidence of squamous cell cancer of the oesophagus (SCCO) in Africa, the history of the disease deserves further examination since it has almost certain significance.

SCCO was of very low incidence in East, Central and Southern Africa until the 1930's (Macvicar, 1925; Strachan, 1934; Berman, 1935; Burrell, 1962; Cook, 1971; Rose, 1979). From that time onward there was a documented rise in incidence over the following decades, first observed in South Africa, reaching 'epidemic' proportions in the fifties and sixties of last century (Ahmed, 1966; Cook, 1971; Gelfand, 1971; van Rensburg, 1981; Bradshaw, McGlashan, & Harington, 1983; Bradshaw & Harington 1987; Wabinga, Parkin, Wabwire-Mangen, & Nambooze, 2000).

There is strong evidence that this was a genuine rise in incidence, not simply a rise in recognition of the disease: post mortem findings in Africa in the early decades of the 20th century (Macvicar, 1925; Strachan, 1934) showed oesophageal cancer to be a rare cause of death at that time, in what have now become very high incidence areas; a continuing rapid rise in incidence was reported after regular monitoring of the incidence of SCCO had begun (Cook, 1971; Bradshaw, McGlashan, & Harington, 1983); there were independent reports of rises in different regions: South Africa (Cook & Burkitt 1971; Rose, 1979; Bradshaw & Harington, 1987), Kenya (Ahmed 1966), Rhodesia (Gelfand, 1971), Swaziland (Keen & Martin, 1971), and Botswana (Macrae & Cook, 1975); a change in the ratio of SCCO to other tumours was also noted, SCCO coming to represent a much greater percentage of all cancers (Bradshaw, McGlashan, & Harington, 1983). These papers provide evidence that this was a genuine and sudden rise in incidence, and indicate that there was an aetiologically significant change which took place in Africa

in the early decades of the 20th century, and is still present, or has had a persisting effect over the course of almost a century.

2. Method

Searches using Medline and Embase were carried using the words: oesophageal or oesophagus, and squamous. These were used in combination with: meta-analysis, Africa, cancer, carcinoma, tobacco, papillomavirus, alcohol, pylori, nitrosamine, polycyclic aromatic hydrocarbon, maize, fumonisin, wood, charcoal, diet, trace element, selenium, zinc, p53, non-acid reflux. No limit was set for year of publication. Data from published research from all continents was considered. Duplicate articles and those with no relevance to aetiology, or neither directly nor indirectly relevant to the disease in Africa were excluded. References were included of other areas of the world with high incidences of SCCO, and with common dietary or environmental carcinogen profiles. References within retrieved papers were followed as appropriate, and relevant archived material was added. Meta-analyses, case-control studies, and studies with large numbers of participants were favoured in assessing evidence.

The literature search provided 263 papers which were assessed as directly or indirectly relevant. These included 32 meta-analyses. These were supplemented with 108 archived or cross-referenced papers. 36 duplicates were excluded. 337 papers were therefore considered in this review, of which 163 are referred to in this paper.

3. Results

3.1 Maize

Within Africa, all high incidence areas have maize as their single staple cereal (Cook, 1971; van Rensburg, 1981) and the source of the bulk of dietary calories.

Maize had been introduced to South Africa by the 17th century. It was in common use in the 19th century, and by 1930 it had become the major food crop in South Africa. By then most small-scale farmers no longer produced cash crops for the market and had begun to depend on maize for subsistence. When first introduced, flint maize was the type grown. White dent was introduced in the late 19th century and by 1930 had become the predominant crop (McCann, 2005).

A major and rapid change took place in the 1920's and 30's which affected processing of maize. Maize had been traditionally stone-ground at home for immediate use. Commercially milled maize had already become available for purchase in big towns, but the mediator of real change was the small-scale hammer mill, also known as the posho mill. These milling units, in Africa first made in 1928, and then produced on an assembly line in East London, South Africa in 1931, were distributed to rural trading stores. Subsistence farmers could have large quantities of maize milled, to take home and use over the course of a few weeks or months. This also became a standard food for migrant labourers, who now carried with them much maize meal, rather than the previous sack of whole maize (Sammon, 2009). Milling of maize involves loss of mineral and vitamin content. Milling also mixes the lipases and oils in the germ and initiates ongoing degenerative processes (Tovey & Hobsley, 2004). Poor and prolonged storage of milled maize accelerates chemical degeneration (Sammon & Whittington, 2009; Lopez-Duarte & Vidal-Quintanar, 2009).

Amongst these changes of type, popularity and processing of grain may lie reasons for the historical rise of SCCO incidence in maize-dependent communities, changes which were first seen in the Transkei region of South Africa, then observed progressively Northwards in Africa. (Oettle, Paterson, Leiman, & Segal, 1986).

A case-control study by Sewram, Sitas, O'Connell and Myers (2014), which did not differentiate between whole maize and other maize products, observed no increased risk of SCCO associated with maize consumption. However in three case-control studies the consumption of maize specifically as maize meal was associated with SCCO risk. Van Rensburg, Bradshaw, Bradshaw, & Rose (1985) found a RR of 5.7 for the daily consumption of purchased maize meal by Zulu men. Controls were well matched for age, referral pattern and urban/rural background. Rossi et al., (1982) in the Veneto region of Italy found a relative risk of 6.17 (3–12.9) for those consuming more than 106g per day of polenta (made from maize meal) against those consuming 0–35 g per day. The controls were well-matched for age. Significantly more cases than controls were farmers. Franceschi, Bidoli, Baron, & La Vecchia (1990) carried out a case-control study in North Eastern Italy. They found a relative risk of 2.1 (1.1–4) for frequent against occasional consumption of polenta. They considered the possible influence of confounding factors but concluded that the effect was genuine. A recent study from Malawi found an OR of 6.6 (2.3–19.3) for the most refined type of maize meal against other types of maize meal (Mlombe et al., 2015). The breakdown of triglycerides that occurs in maize meal (Sammon & Whittington, 2009) identifies maize meal as a food with distinct properties, containing physiologically significant quantities of free fatty acid. In its milled form maize is a potential cause of increased non-acid reflux in communities whose staple food is maize (Sammon &

Iputo, 2006).

3.1.1 Evaluation

Maize has a constant association with SCCO in Africa. There were significant changes in maize processing and usage around 1930, including a move to commercially milled maize. Milled maize meal is chemically different from whole maize. Maize meal has a strong association with SCCO.

3.2 Tobacco

Tobacco is known to contain potent oesophageal carcinogens including polycyclic aromatic hydrocarbons (Hoffman, Hecht, & Wynder, 1983) and tobacco-specific nitrosamines (Stepanov et al., 2014). There is a linear dose-related carcinogenic effect, with worldwide relative risk for smokers of 1.32 to as high as 18.8 (Wynder & Stellman, 1977; Pottern, Morris, Blot, Ziegler, & Fraumeni, 1981; van Rensburg et al., 1985; Yu, Garabrant, Peters, & Mack, 1988; Tran et al., 2005). This has been consistently evidenced in areas of high (Tran et al., 2005; Nasrollahzadeh et al., 2008; Sewram, Sitas, O'Connell, & Myers, 2016), medium (Pottern et al., 1981; Stein et al., 2008) and low incidence of SCCO (Freedman et al., 2007; Steevens, Schouten, Goldbohm, & van den Brandt, 2010; Vaughan, Davis, Kristal, & Thomas, 2016).

In areas of very high incidence the relative risk associated with tobacco has been reported toward the lower end of this spectrum: Iran 1.7 (1.05–2.73)(Nasrollahzadeh et al., 2008); Linxian, China 1.32 (1.15–1.51)(Tran et al., 2005); Transkei South Africa 2.73 (1.33–6.03)(Sammon, 1992); and in these regions there is a significant proportion of SCCO victims who are non-smokers: Iran 78% (Nasrollahzadeh et al., 2008); Linxian, China 36% (Li et al., 1989); South Africa 24%(Sewram et al., 2016). The quantity of tobacco used in very high incidence areas for SCCO has been reported as relatively low (van Rensburg et al., 1985; Segal, Reinach, & de Beer, 1988; Peltzer, 2001).

3.2.1 Evaluation

Tobacco is a significant oesophageal carcinogen. In high risk areas it is used in relatively low quantity, and not used at all by a significant proportion of those with SCCO.

3.3 Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons result from incomplete combustion of plant matter, oil and coal. They are components of the carcinogenic effect of tobacco but are also found commonly in the environment–in water, soil and food. They have shown carcinogenic ability in lung and bladder (P. Gustavsson, A. Gustavsson, & Hogstedt, 1988), breast (Petralia et al., 1999), pancreas and prostate (Nadon, Siemiatycki, Dewra, Krewski, & Gerin, 1995). There is evidence of high environmental levels of PAH in NE Iran, a high incidence area for SCCO (Marjani, Biramijamal, Rakhshani, Hossein-Nezdah, & Malekzadeh, 2010). Similar evidence has been found of high levels of PAH in foods in a high-risk area of China (Roth et al., 1998). High levels of PAH metabolites in the urine of healthy adults were found in the Bomet area of Kenya, an area of high incidence for SCCO. These high PAH levels were associated with indoor cooking (Pritchett et al., 2017).

Abedi-Ardekani et al., (2012) in a case-control study in NE Iran found a significant difference between benzo(a)pyrene staining intensity of non-tumour oesophageal biopsies from SCCO patients and from controls. For the association between SCCO and ascending intensity of benzo(a)pyrene staining they calculated an OR of from 2.42 to 26.6 (5.21–135). Their cases used more opium, more tobacco, were older, and were less educated than controls. Their analysis indicated that a proportion of PAH exposure was from tobacco smoking, with the remainder from other unidentified sources. They advanced their results as evidence of a causal role for PAH in SCCO. The lack of close matching of cases and controls, and the possible increased exposure of cases to PAH from opium smoked for relief of pain caused by their cancer leaves open the possibility of confounding. A study by Islami et al., (2012) of randomly chosen non-smokers in the same area measured PAH metabolites in urine. The main source of PAH was diet. There were associations with red meat and processed meat intake, genetic polymorphism, making bread at home, and second-hand smoking exposure.

Two African studies have a shown an association between cooking on wood or charcoal, and SCCO (Dandara, Li, Walther, & Parker, 2006; Mlombe et al., 2015). Poor control matching makes confounding probable in these studies. However use of open fires for heating and cooking, if they have a direct effect, may be through increased exposure to PAH.

3.3.1 Evaluation

There is no convincing evidence of the involvement of non-tobacco PAH in oesophageal carcinogenesis in high-incidence areas.

3.4 Alcohol

Alcohol has been implicated in many studies and is established as a significant factor in medium and low-risk areas (Segal et al., 1988; Pacella-Norman et al., 2002; Steevens et al., 2010), where it has a greater risk than smoking (Tuyns, 1983). A meta-analysis by Islami et al., (2011) calculated RR's of 2.62(2.07–3.32) and 5.54(3.92–7.28) for moderate and for high alcohol intakes. A synergistic or multiplicate effect has been reported with those who use both alcohol and tobacco (Sumeruk, Segal, Winkel, & van der Merve, 1992; Castellsague et al., 1999; Lee & Wu, 2007; Prabhu, Obi, & Rubenstein, 2009). Sewram (2016) showed a significant association with alcohol consumption in the Eastern Cape of South Africa, a very high incidence area. Home-brewed beer has been consistently proposed as an aetiological agent (Burrell, 1962; Sumeruk et al., 1992; Kachala, 2010) but often found not to have significance in very high incidence areas in Africa and other countries (Bradshaw & Schonland, 1969; van Rensburg et al., 1985; Sammon, 1992; Guo et al., 1994; Parkin, Vizcaino, Skinner, & Ndhlovu, 1994; Tran et al., 2005; Matsha et al., 2006; Nasrollahzadeh et al., 2008). Sewram et al., (2016) argue that the percentage of alcohol in drinks consumed by participants in these studies may have been low and their effect not measurable. In a high-risk area of Iran, a case-control study reported that alcohol was consumed by only 2% of both cases and controls (Nasrollahzadeh et al., 2008).

As with tobacco usage there is a significant minority of those with SCCO in Africa who do not drink alcohol (Pacella-Norman et al., 1992; Sammon, 1992; Parkin et al., 1994; Sewram et al., 2016).

3.4.1 Evaluation

Alcohol may be a contributor to carcinogenesis in high risk areas, but is used in relatively low quantity, and not used at all by a significant proportion of those with SCCO.

3.5 p53

p53 studies offer some evidence with regard to the influence of PAH, tobacco and alcohol There is evidence that higher levels of TP53 mutations within tumours are associated with tobacco usage and with alcohol usage in Japan (Saeki et al., 2002). That study found 17 of 18 tumours in those who both smoked and drank heavily accumulated p53 protein; the OR for the accumulation of p53 protein was 29.8 for this group compared to the non-drinking, non-smoking group with SCCO. Mizobuchi et al., (2000), also working in Japan, confirmed that heavy smokers had a significantly higher overexpression of p53 than moderate or non-smokers (65.4% v38.5% and 44.4%).

A meta-analysis by Wu et al., (2015) which included 20 studies, concluded that there is a positive relationship between heavy smoking and TP53 mutation, OR 2.01(1.12–3.6). This meta-analysis did not include any African studies.

Studies have found that p53 is at lower levels in SCCO in Africa: 42% of 50 tumours in a study from Durban (Chetty & Simelane 1999); 17% of 76 tumours from Transkei, South Africa (Gameldien et al., 1988); 39% of 28 tumours in the Rift Valley, Kenya (Patel et al., 2011); although Matsha et al., (2007) reported a p53 positivity of 70% in a series of 114 SCCO tumours analysed in Cape town. These findings support the possibility that alcohol, nitrosamines and PAH may play a less important role in aetiology in these geographical sites. Furthermore, findings of 89.9% p53 positivity in Golestan, Iran (Abedi-Ardekani et al., 2011), and of up to 87.2% positivity in Linxian, China (Wang et al., 1994; Liang et al., 1995; Cao et al., 2004) suggest that the aetiological factors in these high incidence areas are not all shared with the high incidence areas of Africa.

3.5.1 Evaluation

p53 studies are not conclusive, but would support the contention that heavy smoking and alcohol consumption are not prime carcinogenic influences in high-incidence areas in Africa.

3.6 Human Papillomavirus (HPV) Infection

HPV infection is a worldwide phenomenon. The presence of HPV within SCCO tumours is common but varies in prevalence. There are three historical phases represented in published articles assessing the association between HPV and SCCO. The first phase of assessment of the association included all HPV types and reported the prevalence of HPV within SCCO tumours**.** The second phase followed acceptance that only HPV types 16 and 18 were likely to be relevant to causation and gave rise to reports of lower levels of association when only these sub-types were included (Sitas et al., 2007; Sitas et al., 2012; Liyanage et al., 2013; Schafer et al., 2013; Yong, Xudong, & Lijie, 2013; Hardefeldt, Cox, & Eslick, 2014; Li et al., 2014; Ludmir, Stephens, Palta, Willett, & Czito, 2014; Zhang et al., 2015; Gao et al., 2016; Guo et al., 2016). A third phase of assessment of the association between HPV and SCCO is now current in publications, in which evidence of active HPV infection is sought, together with genetic evidence of aetiological involvement (Ludmir et al., 2014; Koshiol et al., 2010).

In this third phase approach to HPV involvement, Koshiol et al., (2010) examined 272 SCCO tumours from China. Using 'rigorous' techniques, they estimated active infection of tumours with HPV and evidence of oncogenic activity. They found less than 1% HPV presence in the tumours, and no evidence of HPV oncogenic activity. They concluded that they had found little evidence of HPV involvement in the aetiology of SCCO. Halec et al., (2016) were more definite in their rejection of HPV as aetiologically active. They carried out molecular analyses on 133 SCCO tumours which were positive for HPV early proteins. The specimens were from high-incidence areas of Iran, South Africa and China. They found no consistent evidence of viral transformation of the tumours and concluded that SCCO does not follow the HPV-transformation pathogenic model of cervical cancer.

Ludmir et al., (2014) in a review of 7 meta-analyses assessed the evidence for HPV and specifically HPV-16 as a carcinogenic influence on the oesophagus. This meta-analysis did not include any African study. While acknowledging that HPV prevalence correlates strongly with high-SCCO-incidence regions, and that there is an association between HPV and SCCO, they found a lack of evidence of any oncogenic activity or of a clear aetiological association. They concluded that 'regardless of HPV-OSCC infection rates, p16 overexpression and HPV serological data do not support a definitive etiological role for HPV in SCCO'.

3.6.1 Evaluation

If the progressively stringent criteria which are now applied to assessment of the association with HPV is accepted, then HPV does not have a significant role in oesophageal carcinogenesis in high incidence areas of Africa.

3.7 Helicobacter pylori

Helicobacter pylori is highly prevalent in Africa (Segal et al., 2001) where it may infect up to 100% of the population. High levels of H pylori infection have been reported amongst those with SCCO and it has been raised as a possible aetiological agent (Kgomo, Elnagar, Mokoena, Mashoeshoe, & Nagel, 2016; Bohr, Segal, Ally, & Malfertheiner, 2000).

There is considerable variation in the data presented in individual studies, and in assessment of the risk attached to H pylori infection (Islami & Kamangar, 2008). A case-control study by Kgomo et al., (2016) in Pretoria showed a significant association between H pylori infection and SCCO. Their control group comprised patients undergoing gastroscopy for non-cancer indications, and the group had an unusually low H pylori prevalence of 21%. This contrasts with a reported prevalence of 50% to 84% in South Africa as reported by Tanih and Ndip (2013), and implies that this was an inadequately matched group. There are no other African case-control studies available. In Taiwan Wu et al., (2009) found a significant inverse relationship between H pylori seropositivity and SCCO. Whiteman (2012) in Australia found no association. In Germany Venerito et al., (2011) found no association. Cook et al., (2010) reported on a study in Finland which found no association.

International meta-analyses are available which include no data from Africa: Rokkas, Pistolias, Sechopoulos, Robotis, and Margantinis (2007) found no significant relationship between H pylori infection and SCCO, as did Zhou et al., (2008). Xie et al., (2013) found no reliable association between H pylori infection and the risk of SCCO, noting that some studies in Eastern populations showed a reverse relationship. Islami et al., (2008) found no association overall but did find a significant association between H pylori infection and SCCO in Western studies, OR 1.65 (1.17–2.32). Nie, Chen, Yang, Huai, and Lu (2014) agreed with that conclusion with an OR of 1.41 (1.02 to 1.94) for Western studies.

3.7.1 Evaluation

The available evidence does not reliably support H pylori involvement in SCCO aetiology in Africa.

3.8 Nitrosamines

In addition to their established carcinogenic effect in tobacco, nitrosamines are common contaminants in food throughout the world, found in beer in France in amounts of up to 21.3 microgram/Kg (Klein, Girard, Cabarrou, & Debry, 1980), and in bacon up to 139 microgram/Kg (Havery, Kline, Miletta, Joe, & Fazio, 1976). Food-based nitrosamines are carcinogenic to the oesophagus in animal studies (Lijinsky & Taylor, 1981; Rubio, Liu, Chejfec, & Sveander, 1987; Clark et al., 1994; Seto, Kobori, Shimizu, & Morioka, 1994; Fong, Lau, Huebner, & Magee, 1997). In rats, Crampton (1980) found that it required a dose of 132 micrograms/Kg in drinking water, given daily for 900 days, to elicit a carcinogenic response.

Pickled vegetables are commonly eaten in high-risk areas for SCCO in China, and analysis of samples from Linxian has yielded trace amounts of nitrosamines (1.7 and 1.9 microgram/Kg) (Ji & Li, 1991). Comparing contrasting risk areas of Iran, estimation of nitrosamine levels in food showed no unusual levels or geographic differences. Nunn AJ & Nunn JR (1979) found traces (up to 3.2 microgram/Kg) of nitrosamines in food in a high

incidence area for SCCO of South Africa.

N-nitrosamines in gastric juice were measured by Lu (1988) in a high-risk area for SCCO in China. A mean value of 17.09 microgram/Kg was found. There was a positive correlation between the level of nitrosamines and the degree of severity of lesions of the oesophageal mucosa. Lu et al., (1986a) examined urine in a high incidence area (Linxian) and a low-incidence area (Fanxian) in China. They measured N-nitrosamino acids and nitrates, and found significantly higher levels in the subjects from Linxian, indicating higher exposure to N-nitroso compounds and their precursors.

Lu et al., (1986b) showed that human oesophageal cells can be made to undergo malignant transformation by nitrosamine.

A review in 2006 by Jakszyn and Gonzales (2006) assessed the evidence from cohort and case-control studies for an aetiological link between food-related nitrosamines and SCCO. They considered evidence from 61 studies. None of the studies were from Africa. They concluded that insufficient evidence is available so far to link dietary nitrosamines to human oesophageal cancer.

3.8.1 Evaluation

There is insufficient evidence to support an association between nitrosamines and SCCO.

3.9 Fumonisins

The fungal toxins fumonisins were discovered in South Africa in 1988 (Marasas, 2001). The fungus fusarium moniliforme is found in commercial maize throughout the world. 93% of maize imported to the Netherlands from many parts of the world tested positive for its product, fumonisin B1 (de Nijs, van Egmond, Nauta, Rombouts, & Notermans, 1988).

95% of corn-based foods sampled in Argentina contained fumonisin B1 (Solovey, Somoza, Cano, Pacin, & Resnik, 1999). Fumonisin B1 has been detected in commercial corn or corn-based foods in Australia, Brazil, Botswana, Canada, China, Egypt, Italy, Japan, Kenya, Hungary, Nepal, Peru, South Africa, Switzerland, United States and Zimbabwe (Marasas, 1995). Fumonisin contamination of maize is common, particularly in mouldy maize (Yoshizawa, Yamashita, & Luo, 1994). In a medium incidence area of Kwazulu in South Africa 33% of rural maize samples contained fumonisin B, and 33% of volunteers had faecal fumonisin B1 (Chelule, Gqaleni, Dutton, & Chuturgoon, 2001). Similar circumstantial evidence has been found in Iran where rice had significantly higher levels of fumonisin B1 in high incidence areas for SCCO than in low-incidence areas (Alizadeh et al., 2012). Fumonisin B1 contamination of corn in High-risk areas for SCCO was about twice that in low risk areas of China (Yoshizawa 1994; Wang, Wei, Ma, & Luo, 2000). At the time fumonisins were discovered, it was hoped that this might be an aetiological breakthrough, however the circumstantial evidence of higher levels of fumonisins in higher incidence areas for SCCO has not been supported by subsequent research. Feeding large quantities of Fumonisin B1 to rats over a long time gave rise to liver cancers, but no oesophageal cancers (Gelderblom, Kriek, Marasas, & Thiel, 1991). Fumonisin levels in human hair in Transkei, examined by Sewram, Mshicileli, Shephard, & Marasas (2003) were found to be 33 microg/kg hair in the comparatively lower incidence area (Bizana) for SCCO; however in the known higher incidence area (Centane) the level was lower at 27 microg/kg. A study in China using serum sphingolipids as markers of fumonisin exposure in a case control study of SCCO patients found no association between fumonisins and SCCO (Abnet, Borkowf, Qiao, & Albert, 2001).

3.9.1 Evaluation

No study has provided evidence to establish fumonisin as an aetiological agent for SCCO.

3.10 Wild Vegetables

Two papers have drawn attention to risk associated with wild vegetables. A case-control study in Transkei showed an OR of 2.3 (1.09–4.83) for those who consumed Solanum nigrum. Chenopodium album and Amaranthus thunbergii also had significant ORs (Sammon, 1998). Purchase, Tustin & van Rensburg (1975) fed rats on a typical Transkei diet. Addition of two wild vegetables including S nigrum resulted in epithelial cell dysplasia of the oesophagus.

3.10.1 Evaluation

Wild vegetables may be added risk factors for SCCO in localised communities.

3.11 Nutritional Deficiencies

In addition to the association with maize, there have been both environmental and at-risk community dietary associations shown with deficiencies of trace elements–selenium and zinc being the most constant (Burrell, Roach,

& Shadwell, 1966; van Rensburg, 1981; Kibblewhite, van Rensburg, Laker, & Rose, 1984; Schaafsma et al., 2015). Magnesium and riboflavin are also poorly available in a diet based on maize (van Rensburg, 1981). Selenium deficiency is compounded in maize-dependent regions because the majority of selenium in maize is bound as selenomethionine and is not available for intestinal absorption (Beilstein, Whanger, & Yang, 1991).

Zinc deficiency has been shown to promote SCCO development in rats (Taccioli et al., 2012).

Mark et al., (2000) in Linxian China prospectively examined the relation between serum selenium and subsequent death from SCCO. They found an inverse relationship with an OR of 0.56 (0.44–0.71). A study of 218 SCCO patients and 415 healthy controls in China showed significant risk for those on a low selenium diet, and for those on a low zinc diet, OR 0.30 (0.13–0.67) (Lu et al., 2006). In a prospective study in Linzhou, China, Abnet et al., (2005) found that those in the highest quartile of oesophageal tissue zinc concentration were significantly less likely to develop SCCO than those in the lowest quartile HR 0.21 (0.065–0.68).

No population selenium deficiency was found in a high-risk area in Iran (Nouarie et al., 2004). Jaskiewicz, Marasas, Rossouw, van Niekerk, and Heine-Tech (1988) showed an inverse relationship between selenium and oesophageal cytological abnormalities in a high incidence area of South Africa. Hashemian et al., (2017) in Iran found no significant association between SCCE and selenium and zinc levels in toenails.

A detailed analysis of daily per capita micronutrients for African populations was carried out by Schaafsma et al., (2015). Selenium and zinc were both inversely associated with oesophageal cancer incidence, and almost all of the ten highest oesophageal cancer incidence countries had nutrient supplies of Se and Zn less than the adult average requirements.

However in the ‘General Population Trial’ which included 29,584 adults in Linxian, China, the diet was supplemented with four different combinations of vitamins and trace elements which included riboflavin, vitamin E, selenium and zinc, with the hope of reducing the incidence of SCCO. After 25 years the results did not rise to statistical significance (Wang et al., 2017).

Low fruit and vegetable intake are associated with risk for SCCO in Iran (Cook-Mozaffari et al., 1979), and their consumption inversely associated with SCCO risk in China, USA, Japan and South Africa (Sewram, 2014; Yang et al., 2005; Freedman et al., 2007; Yamaji et al., 2008). A meta-analysis by Bo et al., (2015) looked at 20 studies and found a significant inverse relationship between vitamin C intake and SCCO. Wang et al., (2015) in a meta-analysis of citrus fruit intake found an OR of 0.63(0.52–0.75) for highest versus lowest intake of citrus fruit. No studies from Africa were included.

3.11.1 Evaluation

Low intake of fruit, vegetables and trace elements have an association with SCCO, but as yet this is not satisfactorily proven to contribute to causation.

3.12 Non-Acid Reflux

Independent of the search for aetiological agents, has come evidence of a possible aetiological mechanism.

Rat studies have consistently shown that reflux of duodenal content is an initiator of malignancy in oesophageal cells (Miwa et al., 1994; Seto et al., 1994; Ling et al., 2010). In humans there is an established association between atrophic gastritis and SCCO (Hsing et al., 1993; Nyren, 2003; Ye et al., 2004). This association is not dependent on the severity of the gastric atrophy (de Vries et al., 2009).

Iijima et al., (2010) have shown that hypochlorhydria, independent of gastric atrophy, is a significant risk factor for SCCO. In a study of SCCO patients and controls they found a strong association between profound hypochlorhydria and SCCO, with a relative risk of 6.0. The risk was present even after adjusting for the effect of gastric atrophy. Moderate hypochlorhydria showed a statistically insignificant association with SCCO. They suggest that differences in volume and composition of non-acid reflux (NAR) may have a role.

Uno et al., (2011) in a group of superficial SCCOs found a median gastric pH of 4.7 (2.32–6.35), and a significantly greater total reflux and non-acid reflux (NAR) than in the control group. The frequency of NAR was proportional to intragastric pH. The pH of much NAR is within the normal range of pH for the oesophagus, and in Uno et al’s study did not disturb the baseline oesophageal pH. Both Uno et al., (2011) and Iijima et al., (2010) conclude that NAR may play a pivotal role as the causal link between gastric atrophy and SCCO. Both papers suggest that non-acid refluxate may contain carcinogenic content. There is evidence from rat studies of the carcinogenic nature of upper intestinal fluid on the oesophagus, particularly if the refluxate has not been exposed to the neutralising influence of gastric acid (Seto et al., 1994; Yamashita et al., 1998).

Knowledge of what is the normal frequency and pH of gastro-oesophageal reflux has been drawn mostly from Europe, China, Japan and USA (Shay et al., 2004; Zerbib et al., 2005; Zentilin et al., 2006; Xiao et al., 2009; Kawamura et al., 2016). Work in the Eastern Cape of South Africa (Ndebia, Sammon, Umapathy, & Iputo, 2015; Sammon, Ndebia, Umapathy, & Iputo, 2015) has shown increased total and non-acid reflux in a community at high risk for SCCO.

Kgomo, Mokoena, & Ker (2017) found NAR in 73% of their SCCO patients in Pretoria, South Africa. The incidence of NAR in their control group was 22%. They calculated an OR of 8.8(3.2–25.5) for those with NAR in this group.

3.12.1 Evaluation

Non-acid reflux has an association with SCCO. There is evidence to support the contention that the association is causative in high-risk areas.

4. Discussion

Data has been collated from worldwide studies, but is focussed on the aetiology of SCCO in Africa. Carcinogens are present in environments where SCCO thrives, and many of these have come under suspicion, but their aetiological involvement has come to be regarded with caution as more data come to light

Nitrosamines, PAH, fumonisins and H pylori are not newly discovered, and lack of sufficient evidence to associate them with SCCO is not due to a lack of research effort. With the exception of exposure to smoke from open fires, high levels of nitrosamines and PAH have not been reported in Africa. The evidence regarding H pylori does not support the possibility of it as a major carcinogen in Africa. If one or more of these potential carcinogenic influences were principally responsible for the endemic levels of SCCO in some parts of Africa, then in other areas where these hazards are present there should be a commensurate rise in SCCO. However tobacco is a universal health hazard in Africa; wood fire cooking is common throughout the continent; HPV is as prevalent in West Africa as it is in East Africa; nitrosamines are present and often at high levels in food throughout the world. There has not been shown to be a significant concentration of other carcinogens, or a combination of carcinogens which is specific to or exclusive to very high incidence areas. None of these potential carcinogens in the environment - HPV, nitrosamines, H pylori, and fungal toxins - can be advanced as the principal cause of SCCO in very high incidence areas of Africa. Each has, at most, a minor role. Evidence about food related polycyclic aromatic hydrocarbons is incomplete and is complicated by source heterogeneity.

The unreliable association with alcohol in very high incidence areas in Africa and elsewhere, combined with a significant proportion of SCCO victims who do not use alcohol, allows for alcohol to be a factor in a proportion of cases, but not a principal cause of the disease in high-incidence areas.

Tobacco is established as a very significant carcinogen in high incidence areas, but is not used in unusual quantities, and in very high incidence areas there is a sizeable minority of SCCO victims who do not smoke–a minority significant enough to negate the possibility of tobacco usage as the main aetiological agent.

Low dietary selenium, zinc, fruit and vegetables are not exclusive to high risk countries or high risk regions, but may act by increasing susceptibility to oesophageal carcinogenesis.

Genetic studies have not been included in this review. They may usefully indicate susceptibility and may help in understanding the mechanisms involved in a carcinogenic process, but cannot explain an epidemic that arose in one region, and within one generation spread to other regions of differing ethnic background.

There are so far only a few papers evidencing non-acid reflux as a causative mechanism for SCCO, but within these studies the evidence is convincing. There is early evidence of increased non-acid reflux patterns in Africa. Establishing normal and abnormal patterns of reflux and diet in communities throughout East and Southern Africa will aid understanding of local oesophageal physiology and pathology. Study of the content, viability and activity of refluxed small intestinal enzymes in the lower oesophagus in at-risk populations may also provide crucial knowledge.

In the apparent absence of a single responsible carcinogen, there may be a powerful cocarcinogen, or there may be a different type of predisposition which facilitates carcinogenesis by tobacco. The existence of a powerful cocarcinogen becomes less probable as many decades pass without a definite candidate identified. It is then probable that there is a process at work in very high incidence areas which predisposes to carcinogenesis by tobacco. The significant minority of those affected by SCCO in these areas who are non-smokers implies a process which, while predisposing to tobacco carcinogenesis, may either predispose to other environmental carcinogens, or may itself be fully capable of initiating carcinogenic change.

The remarkable history of the disease in Africa supports a direct rather than indirect association with maize consumption. Chemical degeneration of milled maize creates the probability of diet-associated non-acid reflux, which is now recognised as a significant risk factor for SCCO. There is evidence that the deficiencies of vitamins and trace elements in maize-based diets also contribute to an increased risk of SCCO.

5. Conclusion

SCCO in Africa is of complex aetiology. Carcinogens are present in the environment, but not significantly more so in higher than in lower incidence areas. There is no credible candidate for principal oesophageal carcinogen in Africa. Non-acid reflux is emerging as a likely mechanism involved in the carcinogenic process. There is good reason to look again at milled maize: its nutritional deficiencies, potential contaminations, and degenerative processes.

Competing Interests Statement

The authors declare that there are no competing or potential conflicts of interest.

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