Squamous Cancer of the Esophagus in Africa: A Causal Pathway Established

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Abstract

Squamous cancer of the esophagus has been endemic in much of East, Central and Southern Africa since the 1940s. Much research has concentrated on attempts to identify major carcinogenic influences, and failure to do so has made it clear that the problem in high incidence areas (HIAs) is not primarily of potent environmental carcinogens, but of population susceptibility. In Africa the association with maize is constant and strong. Research in the last decade has helped to explain that association. Considered along with historical findings there is now enough evidence to establish causal associations of a nutritionally deficient maize diet and use of maize meal with squamous cancer of the esophagus. Evidence is available in a high incidence area of degenerating maize meal resulting in excess production of PGE2, gastric hypochlorhydria and a predominant pattern of non-acid gastro-esophageal reflux. This pathway explains the existence of major population susceptibility: a poor maize-based diet provides specific nutritional deficiencies and n-6 fatty acid dominance which cause failure of homeostasis of the arachidonic acid cascade; with this background chemically degenerating maize meal then triggers duodenogastric reflux and non-acid gastro-esophageal reflux; non-acid reflux causes squamous cancer of the esophagus. Within a susceptible population, environmental carcinogens including tobacco increase individual risk. There is sufficient evidence that this is an active pathway, and the dominant pathway to SCCE in high incidence areas in Africa. There is sufficient evidence to justify appropriate preventative measures.

Keywords: Squamous cancer- Esophagus- Africa- Etiology- Reflux

Introduction

Squamous cell carcinoma of the esophagus (SCCE) emerged with a sudden explosive rise in incidence in South Africa, spread to much of Southern, East and Central Africa in the 1940s to 1970s, and has remained highly prevalent within parts of the region since then [1-3]. Incidences remain high throughout East, Central and Southern Africa, peaking currently in Malawi. SCCE is a devastating disease in Africa, not amenable to cure or even satisfactory palliation in many of the affected regions.

The association of maize with SCCE in Africa is constant and strong, and has been the subject of speculation and hypothesis for many decades. Lack of certainty about the place of maize in the genesis of endemic SCCE led to a belief that the association may be spurious. The last decade has brought new evidence which clarifies that association. Key new findings have included demonstration of a causal role of non-acid reflux (NAR) in SCCE [4, 5], and demonstration of NAR in an affected community [6].

In this article I piece together strands of historical and recent research and put forward what I believe is no longer a hypothesis, but a satisfactorily evidenced pathway to SCCE, the dominant pathway to SCCE in high incidence areas (HIAs) in Africa, and an impetus for preventive action. The pathway is illustrated with evidence from HIAs.

Non-acid reflux

Two studies have shown evidence of an association between NAR and SCCE. Uno et al [4] in Japan found that NAR episodes were significantly higher in SCCE patients than in controls. The number of NAR episodes
was significantly proportional to intragastric pH level. Kgomo et al [5] in South Africa found significantly more NAR in their SCCE group than in controls. Both these studies concluded that NAR is part of the causal pathway of SCCE (Figure 1).

In related findings Iijima et al [7], also in Japan, found a strong association between SCCE patients and profound hypochlorhydria. They commented that ‘a lower level of gastric acid secretion, especially profound hypochlorhydria, was a strong risk factor for ESCC’ (SCCE). The association between gastric atrophy and SCCE is further diminished by a study showing no increased risk of SCCE with increasing histological changes of atrophy [8] supporting hypochlorhydria as the true risk factor for SCCE.

None of these studies examined the content of the refluxate. Evidence of the insufficiency of isolated NAR to cause SCCE is offered by the fact that proton pump inhibitors promote NAR but their widespread use has not resulted in an epidemic of SCCE in users. Animal studies have consistently shown that upper intestinal juice is strongly mitogenic to the oesophagus and that the combination of reflux of upper GI juices particularly pancreatic juice, in the absence of gastric acid, is a potent agent of squamous carcinogenesis [9, 10].

Maize

In very high incidence areas throughout the world people subsist on a nutritionally deficient monocereal diet of either wheat or maize [1]. In Africa there is a consistent and strong relationship between maize and high incidences [1]. It is of note that there was no significant incidence of SCCE in the nineteenth century in regions where maize was the staple diet [11]. Pellagra and kwashiorkor, diseases that accompany an otherwise deficient maize diet were common at that time [11, 12]. However the upsurge in incidence of SCCE did not occur until the fourth and fifth decades of the twentieth century [13, 14]. There is no evidence of the emergence of a powerful carcinogen accompanying that explosive rise, but there are remarkable historical parallels between emergence of small-scale rural milling technology, the change in dietary predominance from whole maize to maize meal [11], and the sudden growth in SCCE incidence.

Case-control studies within maize-based regions have not identified maize consumption as a risk factor. However several studies in Africa and elsewhere have identified the use of maize in the form of maize meal as conferring a very significant risk of SCCE [15-17]. A study in Malawi showed the strongest association of SCCE with the most highly refined maize meal [18].

Maize and n-6 fatty acid dominance

Linoleic acid (LA), bound in triglyceride form, constitutes most of the fat content of maize. People in HIA of Africa obtain the majority of their calories from maize, and may not choose to or be able to supplement this with sources of n-3 fat with the result that n-6 fatty acids predominate.

Dietary n-6 dominance causes arachidonic acid cascade overreactions throughout the body, which lead to excess conversion of LA to arachidonic acid and arachidonic acid to PGE2 [19].

This shift of the arachidonic acid cascade towards production of PGE2 can be amplified by other dietary deficiencies in regions where the diet is almost exclusively based on maize, and consumed as maize meal products. Maize meal loses up to 60% of its fat content in the milling process. This accentuates the deficiency of n-3 fats. Milling also involves loss of vitamins and trace elements.

The consequences of deficiency of n-3 fatty acids may be augmented by deficiency of selenium [20] and of zinc [21], each of which upregulate COX-2, which in turn increases throughput of LA to PGE2. These deficiencies are common to HIA [22].

Excess production of PGE2 has been found in a HIA in the former Transkei region of South Africa where salivary levels were investigated in a religious community who lived on maize and maize products, and chose not to eat any additional fat. Their salivary PGE2 was significantly higher than people in the same area who consumed a maize-based diet but used added fat regularly, and also significantly higher than the PGE2 level in UK controls eating a western diet [23].

Change of diet from whole maize to milled maize

In the late 1920s and early 1930s small hammer mills became commercially available, at first in the Eastern Cape of South Africa, and were distributed to rural general stores. Rural farmers could bring their maize for milling,
and take home finely ground maize meal. Significant quantities were milled, stored in homes and used over the course of weeks or even months [11]. Maize meal is chemically different from whole maize. The process of milling releases lipases which mix with and react with the fat content resulting in hydrolysis of esterified fatty acids to the free form. This occurs rapidly in maize and in wheat for the first few months after milling [24]. The progressive change to non-esterified fatty acids has been measured as up to 363 mg of free LA per 100g of prepared maize-meal based food [25]. Consumption of 1Kg per day of prepared maize meal or maize flour products provides a daily intake of up to 3.6 grams of non-esterified LA.

Non-esterified LA, when presented to the gastric mucosa is effective in small amounts, and rapid in its action: LA added to rat gastric mucosa cells increased the concentration of arachidonic acid, induced expression of COX-2 and augmented production of PGE2. These were time and dose-dependent increases. COX-2 mRNA was induced 1 hour after LA addition, and was maintained for 24 hours [26]. In a study with human volunteers 3g of LA was administered to healthy human volunteers. They showed a marked rise in both gastric PGE and 13,14-dihydro 15-keto prostaglandin E2 [27].

In a situation of n-6 dominance and arachidonic acid cascade overreaction, these responses to non-esterified linoleic acid may be greatly augmented and the consequences of excess production of PGE2 found.

Evidence from high incidence areas

Fatty acid imbalance is central to the failure of homeostasis of the arachidonic acid cascade. Supplement of the diet with other fats in a HIA has shown a significant protective effect against SCCE in case-control studies. Van Rensburg et al [15] found a reduced risk for those consuming margarine or butter daily. Sammon [28] found a protective effect of total bought fat against SCCE.

Alkali treatment of maize neutralises free fatty acids in maize meal and maize oil, and improves availability of trace elements and vitamins. In major contrast to maize-dependent HIAs of Africa, the incidence of SCCE is low or intermediate in Central and South America countries where an alkali process of nixtamalization is routinely used.

Two foodstuffs made from maize meal (amarewu, a fermented maize meal drink and unQA wethanga, a maize meal and pumpkin dish) caused heartburn in 60% of a sample of users in the former Transkei region. Of these who experienced heartburn 73% regurgitated fluid into the mouth. This was prevented or reduced by aspirin taken 20 minutes before ingestion of the food. This is highly suggestive of a rapid prostaglandin effect [29].

PGE2 reduces acid secretion [30], relaxes the lower esophageal sphincter in a dose -dependent way [31] and relaxes the pyloric sphincter [32]. Inhibition of acid secretion and lower esophageal sphincter relaxation cause NAR. In a HIA gastric juice was aspirated from the gastric fundus of volunteers attending a rural clinic. Half of the samples had a pH over 4. High pH was significantly associated with frequency of maize consumption [33].

Recording of 24hr gastric pH was carried out in asymptomatic volunteers in the Eastern Cape of South Africa. The subjects had a raised median 24-hour pH of 2.84 and a nighttime median pH of 3.7. There were abnormally long periods of nighttime alkalinisation [34].

NAR was predominant in an esophageal impedance study of 77 asymptomatic volunteers in a HIA in South Africa, and there was a higher frequency of gastroesophageal reflux compared with equivalent studies in Europe, China and USA [6].

The study by Kgomo et al [5] cited above was carried out in a high-risk community in South Africa. There was a significant association between NAR and SCCE.

Other factors

Tobacco has a proven association with SCCE in HIAs. The amount of tobacco used is low in some HIAs and there are significant percentages of non-smokers (up to 30% in South Africa) amongst SCCO victims [28, 35]. Alcohol does not have a consistent and clearly established role in HIAs [36]. Many other potential carcinogens have been suggested, including polycyclic aromatic hydrocarbons, and these substances may be active in HIAs, but there is none with consistently proven association [36].

While tobacco is significantly active as a carcinogen in HIAs, the number of non-users of tobacco who have no other known potent carcinogenic influence is high. This makes it probable that, as shown in animal studies [9, 10] NAR with upper gastrointestinal content exerts significant carcinogenic influence on the oesophageal mucosa even when there is no additional carcinogenic agent. A study of 24 hr gastric pH in a HIA found a high pH/gastric alkalinisation and unusually prolonged night-time alkalinisation. There were many rapid alkaline rises. The findings were suggestive of duodenogastric reflux [34]. A case-control study of diet and social factors in a HIA found no association between the cultural habit of self-induced vomiting and SCCO, but noted that the majority of those who used self-induced vomiting regurgitated bile when they vomited, evidence of the prevalence of duodenogastric reflux [34].

Discussion

Hypotheses to explain the very high levels of SCCE in regions of Africa have been put forward over the course of many years. Much research has concentrated on attempts to identify potential carcinogenic influences, and failure to do so has made it more obvious year by year that the problem in high incidence areas (HIAs) is not primarily of potent environmental carcinogens, but of population susceptibility.

The pathway outlined here is now well evidenced and established beyond reasonable doubt as fact, no longer as hypothesis. Evidence has been presented in a HIA of degenerating maize meal, excess production of PGE2, gastric acid suppression, and a predominant pattern of NAR. This pathway is sufficient to explain the existence of major population susceptibility: a maize-based diet provides the necessary nutritionally deficient background;
chemically degenerating maize meal triggers NAR; NAR causes SCCE. 

The evidence is sufficient to justify appropriate preventive measures.

The evidence presented applies widely to areas of East, Central and Southern Africa which depend heavily on maize. SCCE incidence is very high in monocereal cultures in some other parts of the world, and consideration could be given to whether similar mechanisms may be involved.

The importance of chronic micronutrient deficiencies in causing SCCE susceptibility in Africa as emphasized by van Rensburg and van Rensburg [22] needs assessed against inconsistent results from cohort interventions with diet supplements in HIAs in China [37].

In conclusion, there is sufficient evidence to establish causal associations of a nutritionally deficient maize diet and use of maize meal with NAR, and NAR with SCCE. There is sufficient evidence that this is an active pathway and the dominant pathway to SCCE in high incidence areas in Africa. It is no longer necessary that endemic SCCE should persist. The principal causal associations are known, are remediable, and should now be tackled.

References


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