Self-induced vomiting – risk for oesophageal cancer?

T Matsha, A Stepien, E Blanco-Blanco, L T Brink, C J Lombard, S van Rensburg, R T Erasmus

Background. Chronic inflammation of the oesophagus is considered a precursor condition for the development of oesophageal cancer. Identification of the causes of chronic oesophageal irritation is therefore relevant in developing preventive measures. Self-induced vomiting is a cultural practice among the black population of South Africa, particularly those living in the Transkei, a region reported to have one of the highest incidences of oesophageal cancer worldwide.

Methods. We retrospectively examined the association between the practice of self-induced vomiting and the development of cytological features of inflammation in 478 self-selected subjects living in Transkei who underwent early screening for oesophageal cancer. Screening involved brush biopsy, cytological investigation and a questionnaire interview.

Results. The prevalence of self-induced vomiting was 80.5% and 79.1% in males and females, respectively, and this was stable across all ages. Furthermore, self-induced vomiting was found to be significantly and independently associated with oesophageal chronic inflammation (odds ratio 1.83, 95% confidence interval: 1.13 - 2.96, $p = 0.013$).

Conclusion. While the association between the cultural practice of self-induced vomiting and oesophageal cancer has previously been hypothesised, this is the first study to report on an association between this practice and oesophageal chronic inflammation. Further studies that take into account the method used, frequency and duration of vomiting, age of commencement and fasting state of subjects practising self-induced vomiting coupled with accurate indicators of inflammation are needed to elucidate the role of self-induced vomiting in oesophageal pathogenesis.

S Afr Med J 2006; **96:** 209-212.

Self-induced vomiting is a cultural practice among the black population of South Africa, particularly those living in the Transkei, a region reported to have one of the highest incidences of oesophageal cancer in the world.[1,2] The reasons behind this practice are not well understood, but verbal interviews with people from this region have identified the following: (*i*) removal of *inyongo*, which may be explained as detoxification in Western medicine (*inyongo* is characterised by indigestion, lethargy, coated tongue or bitter metallic taste in the mouth and nausea); (*ii*) to cleanse an individual of evil intentionally transmitted by foes, a process strongly recommended by traditional healers; and (*iii*) a regular procedure as part of worship in some Christian cult groups whereby 'holy' water is used instead of traditional medicines to ward off evil. Emetics frequently used are salt water, herbal concoctions or 'holy' water depending on the reasons for the practice. Interestingly, self-induced vomiting is a worldwide phenomenon, for example in subjects suffering from bulimia nervosa (an eating disorder characterised by food bingeing followed by self-induced vomiting).

Recently bulimia nervosa in patients without history of the known aetiological factors has been associated with oesophageal squamous cell carcinoma.[3,4] Self-induced vomiting may be a major insult to the oesophageal mucosa, bathing it in gastric and possibly duodenal juices causing inflammation and a weakened oesophageal epithelium resulting in a condition possibly more favourable to the development of oesophageal cancer. These observations have led the authors to explore the probable association between self-induced vomiting and the induction of inflammation in the oesophagus. In this preliminary investigation we retrospectively analysed data collected between 2002 and 2003 from 478 self-selected subjects living in Transkei, South Africa who underwent early screening for oesophageal cancer. Screening involved brush biopsy, cytological investigation and a questionnaire interview.

Material and methods

Volunteers were recruited from three villages (Mhlakulo, Mpeko and Mbekweni) within a 50 km radius of Umtata, the main urban centre in the Transkei, through an awareness programme emphasising the importance of early oesophageal cancer screening. A consent form and a questionnaire were administered to each individual by the first author (TM). The questionnaire was designed to obtain information retrospectively on known environmental factors such as alcohol

Department of Chemical Pathology, Stellenbosch University, W Cape

T Matsha, PhD
L T Brink, MSc
S van Rensburg, PhD
R T Erasmus, MB BS, FMCPath, DHSM, DABCC, FCPath

Department of Pathology, Walter Sisulu University, Mthatha, E Cape

A Stepien, MB BS, PhD
E Blanco-Blanco, MD

Biostatistics Unit, Medical Research Council of South Africa, Cape Town

C J Lombard, PhD

Corresponding author: *R T Erasmus (rte@sun.ac.za)*

and tobacco consumption and traditional lifestyle that might offer an explanation for the high incidence of oesophageal cancer in the Transkei region. Subjects 18 years or younger, who presented with or who had suffered from swallowing symptoms, and/or who had experienced any symptoms of upper respiratory tract infection in the 3 months before the study, were excluded. Depending on the frequency of self-induced vomiting, each individual was assigned to one of two categories, namely self-induced vomiting 3 times a month, weekly or daily; and self-induced vomiting once a month, seldom or never. Subjects who reported intake of any type of alcoholic beverages such as beer (commercial or home-brewed) and/or spirits were classified in the 'alcohol consumption' category. Similarly, subjects who used cigarettes and/or a pipe, and/or who chewed tobacco were classified as smokers.

Brush cytology of the oesophagus has primarily been used in the identification of precancerous lesions.[5-7] In South Africa brush biopsy screening for oesophageal cancer is done infrequently and irregularly, and is limited to research programmes. A sponge ball compressed in a dissolvable capsule (Nabeya capsule, Japan) was used to collect cytological material as previously described.[6,8] Subjects were brushed in the fasting state between 08h00 and 10h30 am. Briefly, the capsule together with a bundled portion of the attached string was swallowed with water while the subject held the other end of the string. After approximately 10 minutes the brush was slowly withdrawn, inducing exfoliation of the oesophageal mucosal cells, and cytological slides were prepared and fixed immediately using a commercial aerosol fixative (Fencott, Cape Town, South Africa) containing ether, alcohol and polyethylene glycol. The slides were subsequently analysed independently and blindly by a cytologist and pathologist for the presence of chronic inflammation. Individuals with smears positive for the presence of fungal or bacterial infection were excluded from the study. Ethical approval was obtained from the University of Transkei (now Walter Sisulu University) Ethics Committee.

Statistical methods

For categorical data the chi-square test and crude odds ratios (ORs) were used to compare subjects with regard to chronic inflammation. Logistical regression was used to determine the adjusted OR for self-induced vomiting by adjusting for other factors such as age, sex, family history of oesophageal cancer, and alcohol and tobacco consumption. Results were considered significant if *p*-values were less than 0.05.

Results

In total 497 subjects volunteered for early oesophageal cancer screening during the study period. Eleven subjects had incomplete questionnaire data and 8 subjects with fungal inflammation or unidentifiable micro-organisms were excluded, giving a study population of 478 subjects. There were 87 (18.2%) males, with a mean age of 51 ± 17.1 years, and 391 (81.8%) females with a mean age of 48.1 ± 15.3 years. A bias towards females, was observed. Similarly, Erasmus *et al*.[9] encountered an analogous phenomenon in other epidemiological studies conducted in the Transkei population, with females generally volunteering in larger numbers than males, suggesting that females tend to take health issues more seriously than their male counterparts.

Individuals used either one or a combination of methods to induce vomiting, as summarised in Table I. The prevalence of self-induced vomiting was 80.5% and 79.1% in males and females, respectively, and was found to be stable across all age groups (Table II). The effect of self-induced vomiting was studied after adjustments for the other risk factors and was shown to be significantly and independently associated with an increased risk of oesophageal chronic inflammation (OR 1.84, 95% confidence interval (CI): 1.136 - 2.989) (Table III). Surprisingly, alcohol consumption was negatively associated with inflammation (OR 0.62, 95% CI: 0.412 - 0.928); however, the quantity and types of alcoholic beverages were not taken into account in the analysis. While tobacco consumption has been strongly associated with oesophageal cancer in South Africa, it was not associated with inflammation (OR 1.132, 95% CI: 0.702 - 1.824). This may be due to the fact that the duration of smoking, which is the most appropriate exposure measure,[10] was not addressed in the questionnaire.

Discussion

Risk factors that have been reported to play a predominant role in the aetiology of oesophageal cancer include chronic irritation

Table I. Methods used to induce vomiting in subjects with or without inflammation (*N* (%))

Method used	Subjects with inflammation	Subjects without inflammation
Salt water	90 (45.2)	126 (45.1)
Traditional medicine	41 (20.6)	48 (17.2)
Warm water	20 (10.0)	24 (8.6)
'Holy' water	1 (5.5)	3 (1.1)
Vinegar water	4 (2.0)	6 (2.1)

Table II. Prevalence of self-induced vomiting by age and sex

Sex	Age (yrs)	SIV (no) (*N* (%))	SIV (yes) (*N* (%))
Females	< 40	23 (18)	105 (82)
	40 - 60	27 (18.2)	121 (81.8)
	> 60	31 (27.9)	80 (72.1)
Total		81 (20.9)	306 (79.1)
Males	< 40	6 (23.1)	20 (76.9)
	40 - 60	5 (20.0)	20 (80)
	> 60	6 (16.7)	30 (83.3)
Total		17 (19.5)	70 (80.5)

SIV (no) = self-induced vomiting once a month, seldom or never.
SIV (yes) = self-induced vomiting 3 times a week, weekly or daily.

Table III. Relative risk as expressed by odds ratios for various factors associated with chronic inflammation of the oesophagus

Factor	Inflammation prevalence (%)	Crude OR	95% CI	*p*-value*	Adjusted OR	95% CI	*p*-value†
Sex							
Male	41/87 (47.1)	1.31	0.82 - 2.17	0.28	1.38	0.81 - 2.33	0.237
Female	158/391 (40.4)	1.00			1.00		
Age (yrs)							
< 40	63/154 (40.9)	1.00					
40 - 59	75/173 (43.4)	1.11	0.71 - 1.72	0.655	1.10	0.70 - 1.74	0.668
60+	61/147 (41.5)	1.03	0.75 - 1.62	0.918	1.09	0.67 - 1.76	0.728
Vomit							
Yes	168/330 (44.2)	1.71	1.07 - 2.74	0.029	1.83	1.13 - 2.96	0.015
No	31/ 98 (31.6)	1.00			1.00		
FHIST							
Yes	34/65 (52.3)	1.65	0.98 - 2.79	0.078	1.51	0.88 - 2.59	0.131
No	165/413 (40.0)	1.00			1.00		
Tobacco consumption							
Yes	60/137 (43.8)	1.13	0.76 - 1.69	0.608	1.16	0.72 - 1.86	0.555
No	139/341 (40.8)	1.00			1.00		
Alcohol consumption							
Yes	106/276 (38.4)	0.73	0.51 - 1.06	0.110	0.63	0.42 - 0.94	0.023
No	93/202 (46.0)	1.00			1.00		

* *p*-value from Fisher's exact test except for age.
† *p*-value from logistical regression analysis.
FHIST = family history of oesophageal cancer; vomit (no): self-induced vomiting once a month, seldom or never; vomit (yes): self-induced vomiting 3 times a week, weekly or daily.

to the oesophageal mucosa, poverty, nutritional deficiencies, alcohol and smoking.[1,2,10,11] However, alone none of them seems to account for the high incidence rates observed in several high-risk areas and the dramatic variations in the frequency of oesophageal cancer in distinct geographical areas. Comparison of these factors in the different high-incidence areas has shown little in common between areas, but any factor that causes chronic irritation and inflammation of the oesophageal mucosa appears to increase the incidence of oesophageal squamous cell carcinoma.[11] The association between chronic inflammation and a variety of epithelial malignancies has been recognised for centuries, since the observations of Virchow et al.[12] in the 19th century attributing tumour formation to chronic irritation. Chronic inflammation and cancer risk are based on the proximity of two events. One event is the high rate of epithelial cell turnover – as cells turn over, DNA synthesis is required and it is during DNA synthesis that genetic material is more vulnerable to mutation. The second event is the presence of high levels of mutagens within the inflammatory environment, the specific mutagens being reactive oxygen species (ROS) and nitric oxide.[13-15]

This study did not find an association between alcohol intake and/or tobacco consumption and oesophageal chronic inflammation. Substantial alcohol intake, especially in combination with smoking, greatly exposes the oesophageal mucosa to chronic irritation.[11] However, because alcohol consumption and smoking are generally not confined to regions with a high incidence of oesophageal cancer, the irregular distribution of the disease probably reflects a complex interplay between regional practices and genetic factors.

The association between self-induced vomiting and oesophageal chronic inflammation could be likened to the carcinogenic effect of gastro-oesophageal reflux disease (GORD), which is strongly associated with oesophageal adenocarcinoma.[16,17] GORD is characterised by reflux of gastric and duodenal contents into the lower part of the oesophagus, the predominant region for oesophageal adenocarcinoma. Self-induced vomiting, however, may pose a major chronic irritant to the entire oesophagus. Our results suggest that there is a possible association between self-induced vomiting and oesophageal chronic inflammation. However, these preliminary results should be interpreted with caution as the technique used does not differentiate between the various aetiological causes of inflammation such as inflammation due to fungal or bacterial infection. In addition, this is the first study to investigate the possible association between self-induced vomiting and the precursor condition that may predispose individuals to the development of oesophageal cancer. At this stage it is not clear whether the high prevalence (~ 80%) of self-induced vomiting is unique to the Transkei population. Further studies that take into account the method, frequency and duration, age of commencement, and fasting state of subjects practising self-induced vomiting coupled with accurate indicators of inflammation are needed to elucidate the role of

self-induced vomiting in oesophageal pathogenesis.

Based on our preliminary findings, a hypothesis for a chronic inflammation-driven mechanism is proposed as a risk factor for the pathogenesis of oesophageal cancer. The pathogenesis starts from self-induced vomiting either as a means to control weight or as a cultural practice in humans. Gastric acid, bile acids and digestive enzymes induce irritation and inflammation in the oesophagus. The squamous epithelium of the oesophagus responds with inflammatory cell infiltration. Two events in proximity are initiated as a result of inflammation; one is increased DNA synthesis vulnerable to genetic mutations, and the other is the production of ROS by surrounding neutrophils which may cause oxidative stress that is exacerbated by insufficient antioxidants.

We are grateful to the communities of Mbekweni, Umhlakulo and Mpheko for their participation in the study.

This study was funded by grants from the Cancer Association of South Africa and the Medical Research Council of South Africa.

References

1. Bradshaw E, Schonland M. Oesophageal and lung cancers in Natal African males in relation to certain socio-economic factors. An analysis of 484 interviews. *Br J Cancer* 1969; **23:** 275-284.
2. Sammon AM. Case-control study of diet and social factors in cancer of the esophagus in Transkei. *Cancer* 1992; **69:** 860-865.
3. Buyse S, Nahon S, Tuszynski T, Delas N. Bulimia nervosa as a risk factor for squamous cell carcinoma of the esophagus? *Am J Gastroenterol* 2003; **98:** 1442-1443.
4. Dessureault S, Coppola D, Weitzner M, Powers P, Karl RC. Barrett's esophagus and squamous cell carcinoma in a patient with psychogenic vomiting. *Int J Gastrointest Cancer* 2002; **32:** 57-61.
5. Lazarus C, Jaskiewicz K, Southhall HA, Sumeruk RA, Nainkin J. The value of abrasive cytology in the early detection of oesophageal carcinoma. A pilot survey in Ciskei. *S Afr Med J* 1994; **84:** 488-490.
6. Lazarus C, Jaskiewicz K, Sumeruk RA, Nainkin J. Brush cytology technique in the detection of oesophageal carcinoma in the asymptomatic, high risk subject; a pilot survey. *Cytopathology* 1992; **3:** 291 - 296.
7. Roth MJ, Liu SF, Dawsey SM. Cytological detection of esophageal squamous cell carcinoma and precursor lesions using balloon and sponge samplers in asymptomatic adults in Linxian, China. *Cancer* 1997; **80:** 2047-2059.
8. Jaskiewicz K, van Rensburg SJ, Venter FS, Marais C de W. Oesophageal cytological abnormalities in Transkei and possible nutritional influences. *S Afr Med J* 1987; **71:** S3-S4.
9. Erasmus RT, Blanco Blanco E, Okesina AB, Matsha T, Gqweta Z, Mesa JA. Prevalence of diabetes mellitus and impaired glucose tolerance in factory workers from Transkei, South Africa. *S Afr Med J* 2001; **91:** 157 - 160.
10. Launoy G, Milan CH, Faivre J, Pienkowski P, Milan CI, Gignoux M. Alcohol, tobacco and oesophageal cancer: effects of the duration of consumption, mean intake and current and former consumption. *Br J Cancer* 1997; **75:**1389-1396.
11. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003; **349:** 2241-2252.
12. Triolo VA. Nineteenth century foundations of cancer research advances in tumor pathology, nomenclature and theories of oncogenesis. *Cancer Res* 1965; **25:** 75-106.
13. Bagchi D, Bagchi M, Stohs SJ, *et al*. Free radicals and grape seed proanthocyanidin extract: importance in human health and disease prevention. *Toxicology* 2000; **148:** 187-197.
14. Mignogna MD, Fedele S, Russo LL, Muzio LL, Bucci E. Immune activation and chronic inflammation as cause of malignancy in oral lichen planus: is there any evidence? *Oral Oncol* 2004; **40:** 120-130.
15. Orlando RC. Mechanisms of epithelial injury and inflammation in gastrointestinal diseases. *Rev Gastroenterol Disord Suppl* 2002; S2-S8.
16. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF jun. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991; **83:** 2049-2053.
17. Lagergren J, Bergsrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999; **340:** 825-831.

Accepted 22 November 2005.