

## Smoking Habits and Carcinoma of the Stomach: A Case-Control Study

Sisir K. Saha<sup>1</sup>

*Department of Surgery, Queen Elizabeth Hospital, Gateshead, UK*

Over a period of 8 years, a case-control study was carried out on smoking habits in 117 patients with carcinoma of the stomach and 234 controls, and a significant association of a particular method of smoking with the site of gastric carcinoma was found in the cancer patients. Furthermore, there was a highly significant difference in method of smoking between the cancer patients and the control group. The prevalence of smoking habit in the latter was 37%, of which 26% had swallowed the smoke regularly. In contrast, the incidence of smoking habit in the cancer patients was over 56%, of which 64% had swallowed the tobacco smoke. The difference is highly significant ( $P < 0.001$ ). The study also suggests that the distal part, in particular, the antrum of the stomach was affected more frequently among the smokers of the cancer patients who had swallowed the smoke regularly but the cardiac end seemed to be involved more often in the other groups of the cancer patients. These included 'never-smokers,' ex-smokers and those smokers who did not swallow the smoke ( $P < 0.01$ ). It is therefore concluded that the swallowing of tobacco smoke seems to influence the site of gastric carcinoma. The relative risk was six-fold higher among the smokers who did swallow the smoke compared with the 'never-smokers' of the control group.

**Key words:** Stomach — Cancer — Tumor — Etiology — Smoking

Several studies have implicated smoking in the pathogenesis of malignant tumors in certain organs.<sup>1,2)</sup> A variety of carcinogens have been found in appreciable quantities in tobacco, particularly in cigarette smoke.<sup>3-5)</sup> In one study, the effect of cigarette smoke condensate on gastric mucosa grown in organ culture has been found to be consistent with that of the known gastric carcinogens,<sup>4)</sup> but the epidemiological linkage of gastric carcinoma with smoking habit remains inconclusive.<sup>6,7)</sup> Nevertheless, a significant association between the site of gastric tumor and the type of tobacco smoked has been reported.<sup>8)</sup> The fact that carcinoma develops more frequently in the lesser than in the greater curvature of the stomach has been well documented.<sup>9,10)</sup> The tumor has been found equally distributed between the fundus, body and antrum in one study<sup>9)</sup> and more frequently in the antrum than in the other sites of the stomach in another study.<sup>10)</sup> Why carcinoma of the stomach tends to develop in a particular site more often than in other sites is not known. With these facts in mind, a case-control study was set up to look for any correlation of smoking habit with the site of gastric carcinoma. A preliminary report suggested that the proximal part of the stomach was affected more frequently among the non-smokers and the smokers who did not swallow the smoke and the distal part, particularly the antrum, was affected more frequently among the smokers who did swallow the smoke.<sup>11)</sup> The main objective of the case-control study was to see if there was any significant difference from the

control group and to evaluate the relative risk depending on the method of smoking.

### MATERIALS AND METHODS

In the case-control study, patients admitted with a diagnosis of gastric carcinoma were interviewed with a prepared questionnaire. They were told the purpose of the study and requested to avoid inaccurate replies that might affect the results. The questionnaire included marital status, age, sex, occupation and habits of alcoholic intake and smoking and also the details of the age at which the patients had started or discontinued smoking, type of tobacco used, frequency and amount of smoking per day or week and method of smoking. Concerning the last item, the distinction between inhalation of the smoke and swallowing of the smoke into the stomach was carefully explained to each individual. A person was considered to be regular smoker if the person had continued to smoke an average of at least five cigarettes or an equivalent amount of tobacco per day for a period of five years. This included cigar and pipe smoking. Those who had smoked less than five cigarettes per day were excluded from this study. Those who had stopped smoking less than five years prior to interview were regarded as being current smokers and those who had stopped over five years before, as ex-smokers. The diagnosis of carcinoma of the stomach was confirmed by histological examination of the tissue removed at the operation in most instances or postmortem examination in those instances in which patients were unsuitable for surgery. The site of the tumor was determined at the operation, in that the

<sup>1</sup> Present address: 41, Long Close, Bessacarr, Doncaster DN4 7PN, UK.

stomach was divided by arbitrary lines into upper one-third (referred to here as the cardiac end), the middle one-third (body) and the lower one-third (antrum of the stomach). This observation was immediately recorded on the questionnaire forms.

Control subjects were among those patients attending the surgical out-patient clinics with a benign surgical condition. The surgical conditions present in the controls included gall stones, inguinal hernia, enlarged prostate, renal stones, breast lumps and diverticular disease. Subjects were excluded from the control group if they were known to have respiratory, upper gastro-intestinal or vascular diseases. Two controls were selected at random for each cancer patient. They were matched for age (within 5 years), sex, and social class of the cancer patients. When all these criteria were satisfied, they were interviewed to collect data on their smoking habit. They were also told the difference between inhalation and swallowing of the tobacco smoke and the purpose of the data collection.

For statistical analysis, the chi-square test was used to determine the significance of differences; relative risk was estimated from odds ratios along with the 95% confidence intervals, using the Logit method devised by Woolf.<sup>12, 13)</sup>

RESULTS

Over a period of 8 years, 234 controls and 117 patients with gastric carcinoma, aged between 35 and 89 years were included in this study. The age distributions of these two groups are shown in Table I. None of the cancer patients had a past history of pernicious anaemia but in 2 of them gastric carcinoma developed in a benign gastric

ulcer and of 2 other patients, poly a gastrectomy had been performed in one and vagotomy with pyloroplasty in the other one for duodenal ulcer occurring 30 years ago.

Table II shows the demographic data on smoking habits and the sites of gastric carcinoma among the cancer patients. The ratio of male to female was 4.5:1 in the smoking group and 1.12:1 in the non-smoking group. Of the 117 patients, 66 (56.4%) were current smokers. Among these patients, 54 smoked cigarettes and 12 a pipe, though 3 of the latter had initially smoked cigarettes for a few years before they changed to pipe smoking. One patient in the former group had been smoking both cigars and cigarettes all the time. Of the smoking group, 42 patients (63.6%) admitted to having swallowed the smoke regularly but this was denied by the other 24 (36.4%) patients. There seems to be a significant difference in the prevalence of gastric tumor located in the antrum compared with that in the cardiac end in those smokers who swallowed the smoke compared with those who did not or with 'never-smokers'

Table I. Age Distribution of the Cancer Patients and the Controls

Age (years)	Cancer patients (M/F)	Controls (M/F)
31-40	1 (1/0)	2 (2/0)
41-50	2 (1/1)	4 (2/2)
51-60	18 (14/4)	36 (28/8)
61-70	47 (34/13)	94 (68/26)
71-80	41 (26/15)	82 (52/30)
81-90	8 (5/3)	16 (10/6)
Total	117 (81/36)	234 (162/72)

Table II. Distribution of Gastric Carcinoma and the Relative Risk Index with 95% Confidence Intervals

Site of the stomach	Non-smokers		Smokers		OR	Relative risk in swallowing the smoke compared with							
	'Never-smokers'	Ex-smokers	Non-swallowing	Swallowing		Non-swallowing				'Never-smokers'			
						95% confidence intervals	$\chi^2$	P	OR	95% confidence intervals	$\chi^2$	P	
No. (%)	No. (%)	No. (%)	No. (%)										
Cardiac end <sup>a)</sup> (N=46)	13 (46.4)	11 (47.8)	13 (54.2)	9 (21.4)	1					1			
Body (N=24)	6 (21.4)	6 (20.1)	2 (8.3)	10 (23.8)	7.22	1.27-41.01	5.85	<0.02	2.40	0.64-8.98	1.74	NS	
Antrum <sup>a)</sup> (N=47)	9 (32.2)	6 (20.1)	9 (37.5)	23 (54.8)	3.69	1.17-11.61	5.18	<0.05	3.69	1.17-11.61	5.18	<0.05	
Total	28	23	24	42=117									

The Logit method was used to calculate the relative risk index and 95% confidence intervals.

OR=odds ratio, NS=not significant.

a) Contingency  $\chi^2=8.89$ ,  $P<0.01$ , the significance of the difference between the swallowing group and all the other groups combined together.

Table III. Smoking Habits in the Cancer Patients and the Control Group

Smoking habits	Cancer patients		Control group		Relative risk in relation to 'never-smokers'	
	No.	(%)	No.	(%)	Odds ratio	95% confidence intervals
Non-Smokers	51	(43.6)	148	(63.2)		
'Never-smokers'	28	(23.9)	94	(40.2)	1	
Ex-smokers	23	(19.7)	54	(23.1)	1.43	1.74-3.55
Smokers	66	(56.4)	86	(36.8)	2.58	1.22-5.47
Non-swallowing	24	(36.4)	64	(74.4)	1.26	1.49-2.35
Swallowing group	42	(63.6)	22	(25.6)	6.40	3.29-12.48
Total	117		234			

Table IV. Relative Risk in Relation to 'Never-smokers' According to Smoking Dose (Cigarettes per Day)

Site of the stomach	Never-smokers	Number of cigarettes per day					
		10-19		OR	95% confidence intervals	20-30	
		No. (%)				No. (%)	
Cardiac end	13	7 (36.9)	1		9 (25.7)	1	
Body	6	2 (10.5)	0.62	0.90-3.90	8 (22.9)	1.93	0.50-7.46
Antrum	9	10 (52.6)	2.06	0.57-7.46	18 (51.4)	2.89	0.90-9.30
Total	28	19 (100)			35 (100)		

Pipe smokers and ex-smokers not included. OR = odds ratio. The Logit method used to calculate the relative risk index and 95% confidence intervals.

Table V. Relative Risk in Relation to 'Never-smokers' According to the Age at which Smoking Started

Site of the stomach	Never smokers	Age (years) at which smoking started								
		10-15			16-20			21-30		
		No. (%)	OR	95% conf. Int.	No. (%)	OR	95% Conf. Int.	No. (%)	OR	95% Conf. Int.
Cardiac end	13	10 (30.3)	1		14 (35.9)	1		8 (47.0)	1	
Body	6	6 (18.2)	1.3	0.32-5.21	13 (33.3)	2.01	0.59-6.86	2 (11.8)	0.54	0.09-3.34
Antrum	9	17 (51.5)	2.46	0.31-7.79	12 (30.8)	1.24	0.39-3.89	7 (41.2)	1.26	0.34-4.73
Total	28	33 (100)			39 (100)			17 (100)		

OR = Odds ratio, Conf. Int. = confidence intervals. Of the 89 smokers, 23 patients had stopped smoking over 5 years previously. The relative risk is high in the age group between 10 and 15 years compared with the other age groups and excess risk remains in the antrum of the stomach.

( $P < 0.05$ ). There was a four-fold greater relative risk for cancer in the antrum of the stomach (Table II) for patients swallowing the smoke.

The data on smoking habits of the controls and the cancer patients are shown in Table III. The difference in smoking habit is highly significant between these two groups ( $P < 0.01$ ) or between the swallowing group and the non-swallowing group of the smokers or 'never-smokers' ( $P < 0.001$ ). Furthermore, the relative risk for swallowing the smoke appeared to be six-fold greater in

relation to 'never-smokers' of the control group (Table III).

Patients were subdivided according to the tumor sites and the level of smoking per day (Table IV) or the age at which the patients had started smoking (Table V). Although there was no significant difference in the sites of gastric cancer depending on these two risk factors, an excess risk seems to be evident in those who had smoked over 20 cigarettes per day (Table IV) or those who had started smoking at the age of between 10 and 15 years

Table VI. Difference in Smoking Habits between the Manual and Sedentary Working Classes

Occupations	Smokers		Non-smokers	
	No.	Total (%)	No.	Total (%)
<b>Manual workers (N=83)</b>				
Miners in coal and iron industries	20	} =54 (65.1)	7	} =29 (34.9)
Labourers in farming industries (agriculture & fishermen)	5		10	
Labourers in steel plants, forestry road construction, engine & lorry drivers and other industries	28		11	
Labourers in domestic work	1		1	
<b>Sedentary Workers (N=34)</b>				
Office workers	6	} =12 (35.3)	6	} =22 (64.7)
Housewives	3		11	
Miscellaneous	3		5	
<b>Total</b>		<b>66</b>		<b>51=117</b>

Contingency  $\chi^2=8.7$ ,  $P<0.01$ .

(Table V) compared with the other age groups in relation to 'never-smokers.' In both groups, the relative risk is higher in the antrum than in the other sites of the stomach. The instances of smoking and nonsmoking habits were distributed between the manual and sedentary working classes. The difference in smoking habit between these two working classes is highly significant ( $P<0.01$ ) (Table VI). The data on alcoholic intake suggest that 52 patients were non-drinkers, 32 had drinks on social occasions, 17 consumed up to 7 pints of beer per week and the other 17 patients drank over 7 pints of beer per week. The latter two groups represent only 29% of the series. Hence this factor seems unlikely to be a major contributor to stomach cancer. In most instances, poorly differentiated adenocarcinoma of the stomach was found, but in a few cases, intestinal metaplasia was noted in the histology report.

DISCUSSION

It has been documented that gastric carcinoma develops in certain sites more often than in other sites of the stomach<sup>9,10</sup> but the factors responsible for this are not known. Inconclusive results have been reported in studies of ABO blood groups, diet, drink, occupation and smoking habit.<sup>14-18</sup> What seems to be absent from those studies is that the sites of gastric carcinoma were not included in the search for any correlation with the putative contributory factors.

Smoking by inhalation is a common habit, the incidence being 77% in men and 54% in women.<sup>19</sup> A similar trend was also found in male doctors<sup>20</sup> and in the control group of this study. Although the question of swallowing

of the smoke had not been considered in the previous studies, it was pointed out that there were a few smokers who inhaled very little smoke or none at all, the incidence being 23% in men and 46% in women of the general population in one study<sup>19</sup> and 16% in male doctors in another study.<sup>20</sup> Whether these smokers swallowed the smoke instead, was left an open question in both studies. The fact that smokers do also swallow the smoke has not been highlighted in any report in the literature, but 26% of the smokers in the control group and 64% of the smokers among the cancer patients included in this study were found to have swallowed the smoke regularly. The difference between these two groups is highly significant ( $P<0.001$ ) (Table III). Furthermore, the relative risk for gastric carcinoma was six-fold higher among the smokers who swallow the smoke regularly compared with the 'never-smokers.' It is apparent that the antrum of the stomach in the same group is affected more frequently than the cardiac end ( $P<0.05$ ) (Table II); the difference becomes highly significant ( $\chi^2=8.89$ ,  $P<0.01$ ) if 'never-smokers' ex-smokers and non-swallowing smokers are included in one group and swallowers in another group. This suggests that swallowing of the smoke carried an excess risk in developing carcinoma in the antrum. The risk seems to be four fold compared with the cardiac end in relation to 'never-smokers' or non-swallowing smokers (Table II).

Gastric carcinoma located in the body of the stomach seems to be equally distributed between smokers and nonsmokers, but the incidence was apparently greater in swallowing than in nonswallowing smokers. This is statistically significant ( $P<0.05$ ). Despite a careful assessment, possible sources of bias could not be ruled out

in the distribution of gastric tumors. It is therefore rational to include those tumors present in the cardiac end in one group and those in the body and antrum in another group. This rearrangement overcomes possible sources of bias in relation to those tumors included in the body. Of the 66 smokers, tumors were found in the cardiac end in 22, and in the body and antrum in 44. A similar redistribution could be made among the non-smokers. The difference is highly significant ( $\chi^2=7.37$ ,  $P<0.01$ ) between swallowing and non-swallowing habit in the smokers group and significant ( $\chi^2=5.15$ ,  $P<0.05$ ) between the swallowing group and 'never-smokers' (Table II). Apart from the smoking habit, the effect of type of tobacco smoking was also investigated. In the literature, pipe smoking was shown to be correlated with the site of gastric carcinoma but pipe smokers were the most prevalent among the cancer patients included in that study.<sup>8</sup>) Furthermore, method of smoking was not taken into account in that study. In sharp contrast, cigarette smoking was the most common habit among the cancer patients of this study. Therefore, no conclusion could be reached as to the effect of a particular type of tobacco used by the cancer patients upon the site of gastric tumor. The reason why the cardiac end of the stomach is affected more often among the non-smokers and non-swallowing group of the smokers has yet to be explained. In the latter, there remains a possibility that carcinogenic agents derived from the unburnt tobacco dissolved in the saliva and entered the stomach, and some tobacco smoke might have entered the proximal part of the stomach, despite the claim made by the cancer patients that they had not swallowed smoke. In the case of 'never-smokers,' obviously other factors are involved.

Alcoholic drink was found to be unrelated to gastric carcinoma in this study, which is in agreement with other studies.<sup>16, 21</sup>) Dietary factors have been investigated with inconclusive results,<sup>14, 16, 17</sup>) though diet has been implicated in the aetiology of stomach cancer in recent literature.<sup>21, 22</sup>) The results of these studies provide a source of much debate and controversy. A cautious approach is necessary in interpreting the data even though no particular risk factor has yet been identified in those studies. A similar observation has been made in a comprehensive review.<sup>23</sup>) The fact that stomach cancer develops more frequently among the poorer section of the community has been well recognized. In the general

population, there is a distinct difference in trend in smoking habit between the manual working and professional classes, in that the incidence is 42.5% (49% in men and 36% in women) in the former and 16% in the latter group.<sup>24</sup>) In contrast, the incidence of smoking habit was 65% in the manual and 35% in the sedentary working classes among the cancer patients (Table VI). The difference between these two groups is highly significant. Hence, the gastric carcinoma found in the poorer section of the community may be a consequence of smoking habits and is probably not related to standard of living.

The associated odds ratio in smoking habits between the cancer patients and the control group of this study is 2.23, which is very unlikely to imply a casual relationship, as a result of possible sources of bias. The latter could be discounted by further evidence, in that the incidence of smoking in the general population over the age of 20 years was reported to be 33.6%<sup>24</sup>) which seems to be consistent with that in the control group of this study. Although the overall relative risk for stomach cancer seems to be fairly small in this study, there was a high relative risk for those smokers who had swallowed the smoke regularly. The risk remains no different in the non-swallowing group of the smokers from the 'never-smokers,' but it seems to be slightly higher in the ex-smokers than in the non-swallowing group. This difference could be explained by the fact that many of the ex-smokers did swallow the smoke, the effect of which would continue for some time even though smoking was discontinued for more than 5 years. Apart from method of smoking, there is also evidence to suggest that the antrum of the stomach would be affected more often if the patients continued to smoke over 20 cigarettes per day (Table IV) or had started smoking at an age between 10 and 15 years (Table V). These results provide clues for further research on the aetiology of gastric carcinoma.

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