

# EVALUATION OF CANCER RISK IN TOBACCO CHEWERS AND SMOKERS: AN EPIDEMIOLOGIC ASSESSMENT

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A retrospective study of cancer at high risk sites in the region of the head and neck was undertaken at the Bombay Cancer Registry, in 1968, to evaluate the effects of tobacco when chewed or smoked. There is sufficient evidence available today to indict chewing and smoking of tobacco as factors of great importance in the etiology of oral, pharyngeal, laryngeal, and esophageal cancers—the most common sites affected by the disease in Greater Bombay. This cause/effect association is probably as intimate as that of cigarette smoking and lung cancer. The carcinogenic action of chewed tobacco is particularly evident at those sites where the bolus is retained in place for any length of time. Likewise, inhalation of tobacco fumes during the act of smoking produces a stream of gas and of solid particles which impinges directly on the oropharynx and especially on the soft palate initially and exposes smokers to the increased risk of developing cancer at exactly these posterior sites in the oropharynx, rather than more anteriorly in the oral cavity where the tissues do not directly bear the brunt of the onslaught from the smoke. It is revealing to find that the high risk sites involved in tobacco chewers appear to be the least affected in smokers, and vice versa.

WITH THE ESTABLISHMENT OF THE BOMBAY Registry in 1963, reliable morbidity rates began to be obtained for the first time from an Indian population and revealed the magnitude of the total cancer problem in the country. All previous Indian reports were based on a study of frequency ratios from isolated hospital records. A precisely outlined population of over 5,500,000 persons, resident within the strict geographical limits of Greater Bombay, has since been kept under surveillance, and

because of the heterogenous nature of the inhabitants, representative of all the States in the Union, the Bombay data can be considered to represent a typical Indian sample.

A retrospective study of cancer at high risk sites in the region of the head and neck was undertaken in 1968, to evaluate the statistical significance if any, of the varying effects of tobacco when chewed and smoked. Some interesting conclusions drawn from this preliminary study appear to be of sufficient importance to merit adequate notice.

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## INCIDENCE RATES AND FREQUENCY RATIOS

The incidence rates estimated at Bombay, confirm that in a major Indian urban centre, cancers of the buccal cavity, pharynx, larynx and oesophagus present a grave problem, as severe as any reported in literature.<sup>1,3</sup> Frequency-ratio studies based on individual hospital records throughout India, also show that Indians on the whole appear to face a high risk of developing cancer at these sites.<sup>5,8</sup>

## SUSPECTED ETIOLOGIC FACTORS

1. The high incidence of buccal and pharyngeal cancer in India has been traditionally

believed to be due to the habit of chewing a quid called "pan" consisting of a green leaf\* (Fig. 1) in which are rolled sliced betel-nut, tobacco dust, slaked lime, liquified catechu, and varying amounts of a number of spicy ingredients.<sup>4-7</sup> In association with a pungent diet, poor oral hygiene, and malnutrition, this combination appears to lead to the development of cancer in the above-mentioned areas.

2. Esophageal cancer is another problem of great importance, as it is the most common gastrointestinal cancer seen in Bombay. One of the well-known characteristics of esophageal cancer is the male bias noted in sex-ratios throughout the world. Greater Bombay, however, presents a surprisingly low M:F ratio at this site. The reasons for this unusual near-equal, sex incidence are not yet clear and await the outcome of investigations currently in progress at the Bombay Registry. The situation perhaps indicates a common environmental or dietary etiology in the two sexes. There is some evidence in our data to support the view that tobacco may also stand indicted in the etiology of esophageal cancer.

3. Common etiologic factors are largely responsible for cancer arising in the "oropharynx and larynx," the most important by far being tobacco smoke. The volume and type of tobacco contained in the cigarette or bidi (which factors are responsible for the temperature at which it burns), most likely decide whether the mucosa in the lower or the upper respiratory tract in smokers bears the brunt of the chemical onslaught by the carcinogens produced by the burning tobacco. The volume of smoke produced at each draw and the

\* The leaf used in making the quid is obtained from the "betel vine (piper betel)" tree.

associated depth of inhalation seem to be the two other factors that decide this issue.

4. Likewise, the habit of chewing tobacco either as such or mixed with various ingredients is probably the common denominator responsible for the high incidence of cancer in various parts of the "oral cavity," anatomically situated more anteriorly.

#### METHODOLOGY

All patients afflicted by cancer in Greater Bombay, and admitted to the wards of various hospitals, are individually interviewed in person. Only those patients who had available histologic proof of cancer were included in this study. This investigation was further restricted to patients who had lesions only involving the oral cavity, pharynx, esophagus, and larynx (international list numbers 140 through 148, 150 and 161). Malignant neoplasms arising in the salivary glands, and unspecified areas of the 4 sites, viz. tongue, palate, mouth, and pharynx were excluded from this investigation.

In order to evaluate the probable etiologic factors affecting various sections of the Greater Bombay population, a sample of the city's residents was chosen from the registered voters' list maintained by the Collector of Bombay to serve as a control group. These persons were then matched for age, sex, and religion, with the cancer patients under study.

Our results thus relate to 2,005 cancer patients, compared with 2,005 matched controls. The method adopted in selecting our controls from the total sample assured the choice of a group of people exactly comparable in age, sex, and religion with the cancer sample.



FIG. 1. Preparation of pān. Left to right: 1. betel leaf, 2. betel leaf + lime, 3. betel leaf + lime + tobacco + other ingredients, 4. betel nut, 5. rolled pān pinned with a clove.

TABLE 1. Relative Risk of Developing Oral, Pharyngeal, Laryngeal, and Esophageal Cancers among Chewers and Smokers at Each Anatomical Site

Site-group	Chewing Habit				Smoking Habit							
	(Assuming risk among non-chewers to be unity)				(Assuming risk among non-smokers to be unity)							
	Cancer cases		Control group		Cancer cases		Control group					
	Non-chewers	Chewers	Non-chewers	Chewers	Non-smokers	Smokers	Non-smokers	Smokers				
				Relative risk	$\chi^2$			Relative risk	$\chi^2$			
Cancer group	853	1152	1340	665	2.7	237.7***	800	1205	1446	559	3.9	421.1***
Lip	8	6	1340	665	1.5	0.2 NS	8	6	1446	559	1.9	0.9 NS
Ant. 2/3 tongue	36	54	1340	665	3.0	26.3***	53	37	1446	559	1.8	6.8**
Floor mouth	10	4	1340	665	0.8	<0.01 NS	6	8	1446	559	3.5	4.5*
Alveolus	26	44	1340	665	3.4	25.2***	43	27	1446	559	1.6	3.3 NS
Buccal mucosa	42	160	1340	665	7.7	164.2***	127	75	1446	559	1.5	7.2**
Hard palate	7	14	1340	665	4.0	9.0**	12	9	1446	559	1.9	1.6 NS
Oral cavity	129	282	1340	665	4.4	178.3***	249	162	1446	559	1.7	21.1***
Base tongue	175	187	1340	665	2.2	44.7***	76	286	1446	559	9.7	346.9***
Soft palate	35	18	1340	665	1.0	<0.01 NS	9	44	1446	559	12.6	73.1***
Tonsils	99	128	1340	665	2.6	47.0***	55	172	1446	559	8.1	210.2***
Oropharynx	309	333	1340	665	2.2	71.6***	140	502	1446	559	9.3	510.5***
Nasopharynx	10	7	1340	665	1.4	0.2 NS	8	9	1446	559	2.9	4.1*
Hypopharynx	21	49	1340	665	4.7	39.0***	36	34	1446	559	2.4	13.2***
Larynx	246	314	1340	665	2.6	96.3***	197	363	1446	559	4.8	257.8***
Esophagus	138	167	1340	665	2.4	52.6***	170	135	1446	559	2.1	33.0***

The  $\chi^2$  values marked with single, double, and triple stars were found to have  $P < 0.05$ ,  $P < 0.01$ , and  $P < 0.001$ , respectively, while those marked "NS" were found to be not significant with  $P > 0.05$ .

RESULTS

We have analyzed our data to evaluate the different effects of tobacco when chewed and smoked on the incidence of cancer at individual sites in this anatomical region.

In the various histograms presented, the values marked with a single asterisk (\*) were found to be significant with  $P < 0.05$ , and those marked with double asterisk and triple asterisk were estimated to have  $P < 0.01$  and  $P < 0.001$ , respectively.

The relative risks of developing cancer at each individual site are shown in Table 1. It is interesting to note that the high risk sites among tobacco chewers appear to be relatively low risk sites among smokers, and vice versa.

The habit of chewing "pān" (with tobacco and other ingredients) has been found to be strongly associated with the high incidence of "oral" cancers. (Sites which do not come into any prolonged contact with the quid, e.g., the lip and the floor of the mouth, do not show any significant association with this habit.)

Smokers on the other hand, show a statistically significant increase in the incidence of cancer in the region of the soft palate, base of the tongue, oropharynx, and larynx. The lip, alveolus, and hard palate seem to be spared in this group. Smoking thus seems to be increasingly implicated as a causative factor in the development of cancer in the "oropharynx and larynx." Thus a reverse site-pattern is revealed, when we tabulate chewing and smok-

ing habits with the different anatomical locations of cancer as it occurs in the region of the mouth and throat (Fig. 2).

Our data show that chewing is increasingly indicted in cancers which arise in the oral cavity and hypopharynx, whereas smoking leads to oropharyngeal and laryngeal cancers (Table 2). When chewers or smokers are further subdivided into those who are addicted to both habits and others who refrain from this double addiction, cross tabulation reveals significantly higher occurrence of cancer in the "twin" habit addicts, in all the regions under study, viz. oral cavity, oropharynx, hypopharynx, larynx and esophagus, in contrast to those addicted to only one habit (Fig. 3), who show a predilection to develop cancer either in the anterior or posterior regions of the mouth and throat, depending upon the type of individual addiction.

When patients were tabulated according to their addiction or abstinence from chewing tobacco, it became obvious that *chewing* was the important factor concerned in initiating oral cancers (Fig. 4). Thus, the risk of developing oral cancer in chewers was found to be 4.8 times higher than in non-chewers, and those who chewed the betel quid without tobacco, only showed 3 times greater risk of developing such cancers than the non-chewers (Table 3).

Site analysis of cancers arising in those smokers addicted to either "bidis," cigarettes, or both showed that smoke from the Indian

FIG. 2. Relative risks of developing oral, pharyngeal, esophageal, and laryngeal cancers at various anatomical sites among chewers and smokers. The values marked with single, double, and triple stars were found to be significant with  $P < 0.05$ ,  $P < 0.01$ , and  $P < 0.001$ , respectively.

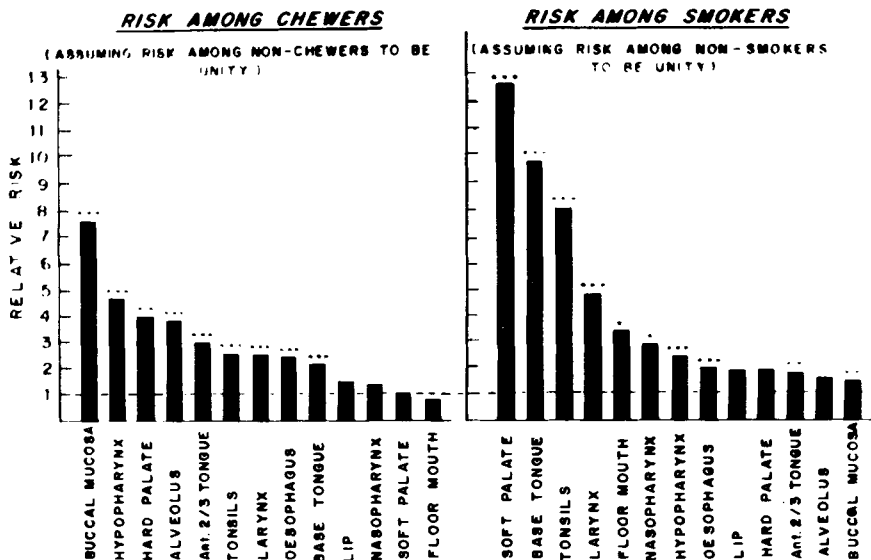


TABLE 2. Relative Risk of Developing Oral, Pharyngeal, Laryngeal, and Esophageal Cancers by the Habit of

Site-group	Chewing Habit				Relative risk	$\chi^2$	Smoking	
	Cancer cases		Control group				Cancer cases	
	No habits	Chewers only	No habits	Chewers only			No habits	Smokers only
Cancer group	243	557	925	521	4.1	231.5***	243	610
Oral cavity	57	192	925	521	6.0	145.4***	57	72
Oropharynx	49	91	925	521	3.3	44.0***	49	260
Nasopharynx	4	4	925	521	1.8	0.2 NS	4	6
Hypopharynx	8	28	925	521	6.2	24.5***	8	13
Larynx	55	142	925	521	4.6	92.1***	55	191
Esophagus	70	100	925	521	2.5	32.4***	70	68

The  $\chi^2$  values marked with single, double, and triple stars were found to have  $P < 0.05$ ,  $P < 0.01$ , and  $P < 0.001$  respectively, while those marked with "NS" were found to be not significant with  $P > 0.05$ .

"bidi" appears to give rise to cancers mainly in the oropharynx and larynx and to a lesser extent in the hypopharyngeal, esophageal, and oral regions (Fig. 5). The risk of developing oropharyngeal cancers among those who only smoke "bidis" was found to be 14 times higher than among non-smokers.

On the other hand, cigarette smoking was apparently found to be responsible for the occurrence of oropharyngeal cancers alone (in this region) and did not seem to affect other areas in the upper respiratory tract (Table 4).

#### DISCUSSION

Results of this preliminary study indicate that tobacco when chewed or smoked is an important contributory factor in the etiology of oral, pharyngeal, laryngeal, and esophageal cancers—the most common sites affected in the Greater Bombay population, and, in effect, throughout India.

#### TOBACCO CHEWING HABIT

The risk of developing cancer in the buccal mucosa was found to be 7.7 times higher in chewers than in non-chewers. Cancer of the buccal mucosa was moreover predominantly found to arise in those habituated to retain the quid in the buccal groove, from a few minutes at a time to overnight. As has been observed by other investigators<sup>2, 9</sup> also, the exact site affected by cancer is the one where the quid is retained for some length of time. However, even when the quid is physically not retained in one position, cancer arises with great frequency in the buccal mucous membrane of tobacco chewers, irrespective of this factor also.

It is obvious that in "chewers," maximum contact with the ingredients of the pulped quid would naturally be maintained by the buccal mucous membrane, because when tobacco is chewed, the resultant extract so ob-

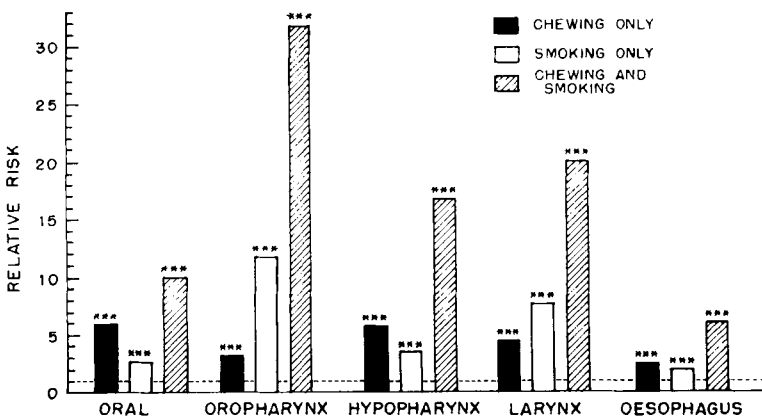


FIG. 3. Relative risk of developing oral, pharyngeal, laryngeal, and esophageal cancers from smoking and chewing (assuming risk among persons with no habits to be unity). The values marked with single, double, and triple stars were found to be significant with  $P < 0.05$ ,  $P < 0.01$ , and  $P < 0.001$ , respectively.

Chewing, Smoking, and a Combination of Both (Assuming Risk among Persons with No Habits to be Unity)

Habit				Chewing + Smoking Habits					
Control group				Cancer cases		Control group			
No habits	Smokers only	Relative risk	$\chi^2$	No habits	Chewers+smokers	No habits	Chewers+smokers	Relative risk	$\chi^2$
925	415	5.6	342.5***	243	595	925	144	15.7	652.7***
925	415	2.8	31.7***	57	90	925	144	10.1	186.6***
925	415	11.8	291.4***	49	242	925	144	31.7	543.1***
925	415	3.3	2.7NS	4	3	925	144	4.8	2.9NS
925	415	3.6	7.8**	8	21	925	144	16.9	72.3***
925	415	7.7	189.8***	55	172	925	144	20.1	390.8***
925	415	2.2	18.2***	70	67	925	144	6.2	103.2***

tained gets mixed with the saliva and remains for a considerable time in the vestibule of the mouth (and not in the floor of the mouth), thereby leading to prolonged contact with the buccal mucosa, even when the quid itself is not physically retained there.

The same argument holds in the case of the hard palate, the alveoli, and the anterior two thirds of the tongue, but, evidently, here contact with the liquid extract can only be maintained for a much shorter duration and cancer occurs with less frequency at these sites than in the buccal mucosa. Cancer was also found to arise more commonly along the lateral borders of the anterior two thirds of the tongue than at the tip or on the dorsum.<sup>8</sup> This is also understandable, as the lateral borders of the anterior part of the tongue are exposed to a greater extent to the carcinogens produced by chewing the quid because they abut on the

vestibule of the mouth. Another factor of great significance at this site (lateral borders of the tongue) is possible exposure to constant irritation by sharp, carious, and dirty (infected) teeth.<sup>8</sup>

An interesting fact arising from this investigation is that the oropharynx and esophagus show high risks in those who chew the betel quid without tobacco. The reason for this seemingly surprising and contradictory finding appears to be due to the fact that tobacco chewers habitually spit out from time to time the resultant liquid extract produced by chewing, and thus naturally are liable to run lesser risks at anatomical sites situated posteriorly in the oropharynx and in the esophagus, as these parts then do not come into contact with the liquified extract expressed from the quid which is retained mainly in the mouth cavity situated as it is more anteriorly before being

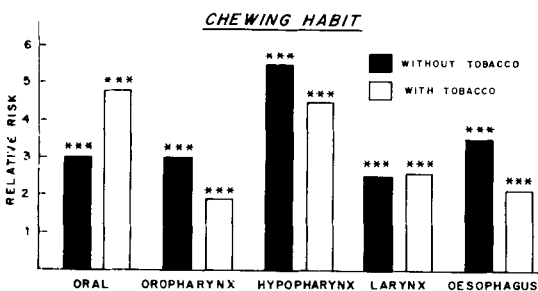


FIG. 4. Relative risk of developing oral, pharyngeal, laryngeal, and esophageal cancers from chewing tobacco. The values marked with single, double, and triple stars were found to be significant with  $P < 0.05$ ,  $P < 0.01$ , and  $P < 0.001$ , respectively.

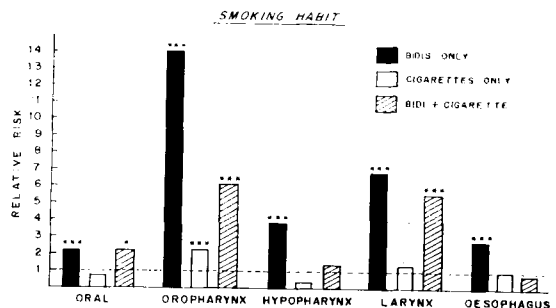


FIG. 5. Relative risk of developing oral, pharyngeal, laryngeal, and esophageal cancers from smoking. The values marked with single, double, and triple stars were found to be significant with  $P < 0.05$ ,  $P < 0.01$ , and  $P < 0.001$ , respectively.

TABLE 3. Relative Risk of Developing Oral, Pharyngeal, Laryngeal, and Esophageal Cancers from Chewing Tobacco

Site-group	Habit of Chewing Quid							
	Cancer cases		Control group		Relative risk	$\chi^2$	Cancer cases	
	Non-chewers	Chewers without tobacco	Non-chewers	Chewers without tobacco			Non-chewers	Tobacco chewers
Cancer group	853	291	1340	152	3.0	106.6***	853	861
Oral cavity	129	44	1340	152	3.0	33.2***	129	238
Oropharynx	309	106	1340	152	3.0	64.1***	309	227
Nasopharynx	10	4	1340	152	3.5	3.3 NS	10	3
Hypopharynx	21	13	1340	152	5.5	24.3***	21	36
Larynx	246	70	1340	152	2.5	33.6***	246	244
Esophagus	138	54	1340	152	3.5	49.3***	138	113

The  $\chi^2$  values marked with single, double, and triple stars were found to have  $P < 0.05$ ,  $P < 0.01$ , and  $P < 0.001$ , respectively, while those marked "NS" were found to be not significant with  $P < 0.05$ .

spat out. However, betel chewers who do not include tobacco in the quid often swallow the juice (without tobacco) which then comes into direct contact with the oropharynx and esophagus, thereby leading to the higher risk of cancer arising at these sites. Thus, even without the tobacco content the quid evidently contains other milder carcinogens or co-carcinogens.

#### SMOKING HABIT

On analyzing the situation critically, it seems logical to expect that when tobacco

smoke is inhaled the stream of smoke consisting of particulate and gaseous chemicals impinges at first directly on the soft palate and then proceeds to envelope the oropharynx, tonsils, and base of the tongue. Analysis of our data reveals that smokers do indeed develop cancers with great frequency exactly at these anatomical sites, with the soft palate taking the brunt of the onslaught and pride of place in frequency rating. Oral cavity sites, situated more anteriorly, may be expected to be less directly affected by tobacco smoke and our investigation does show a much lesser incidence of cancer from this cause, in this more

TABLE 4. Relative Risk of Developing Oral, Pharyngeal, Laryngeal, and Esophageal Cancers from

Site-group	Bidi Smokers				Relative risk	$\chi^2$	Cigarette	
	Cancer cases		Control group				Cancer cases	
	Non-smokers	Bidi smokers	Non-smokers	Bidi smokers			Non-smokers	Cigarette smokers
Cancer group	800	979	1446	310	5.7	531.3***	800	129
Oral cavity	249	120	1446	310	2.3	40.8***	249	22
Oropharynx	140	424	1446	310	14.1	650.4***	140	45
Nasopharynx	8	8	1446	310	4.7	9.2**	8	1
Hypopharynx	36	30	1446	310	3.9	30.6***	36	2
Larynx	197	291	1446	310	6.9	341.0***	197	36
Esophagus	170	106	1446	310	2.9	61.8***	170	23

The  $\chi^2$  values marked with single, double, and triple stars were found to have  $P < 0.05$ ,  $P < 0.01$ , and  $P < 0.001$ , respectively, while those marked "NS" were found to be not significant with  $P > 0.05$ .

(Assuming Risk among Non-chewers to be Unity)

Control group			
Non-chewers	Tobacco chewers	Relative risk	$\chi^2$
1340	513	2.6	190.2***
1340	513	4.8	187.4***
1340	513	1.9	41.1***
1340	513	0.8	<0.01 NS
1340	513	4.5	32.3***
1340	513	2.6	85.6***
1340	513	2.1	31.0***

anteriorly situated region. The incidence of cancer thus runs parallel to the expected risks to which the various sites are exposed in tobacco chewers and smokers.

Unlike the cigarette, the "Indian bidi" (Fig. 6) contains only a small amount of tobacco dust, rolled in a dried leaf, usually of the Temburni tree (*Diospyros melanoxylon*) and occasionally of a few other varieties depending on the region of the country where the bidi is manufactured as a cottage industry, by tens of thousands of villagers working at home. The amount of tobacco content of the "Indian bidi" varies from 0.2 g to 0.3 g, in

comparison with the 1 g of tobacco contained in a standard sized cigarette (king size and super kings contain even more). Furthermore, the cut of the tobacco used in a cigarette is much finer than in the bidi. The bidi cannot be expected to create an equivalent amount of smoke because of its small size. The cut and amount of tobacco also decide to what extent the smoke produced by its ignition can affect the upper or lower mucosa of the respiratory tract. (It is also evidence that the small volume of smoke produced from the Indian bidi cannot be expected to reach down to the bronchi in any concentration and thus can not be expected to affect the mucosa in this region as much as cigarette smoke appears to do.)

Voluminous reports are available to show the highly significant association of cigarette smoking with lung cancer, but not with cancer higher up the respiratory tract, to a like degree. This is so probably because tobacco smoke maintains contact with the palate, base tongue, tonsils, and larynx only for a short time in those who inhale the smoke deeply such as cigarette-smokers (in contrast to cigar and pipe smokers), and its effect is thus more evident lower down the respiratory tract, in the bronchi, where the smoke and tobacco tar finally get trapped and are able to maintain much longer contact with or are adsorbed by the endothelial lining. The length of time of contact with the tar and nicotine products in the tobacco smoke thus seems to be the crucial factor in deciding where the cancer arises.

Smoking Bidi, Cigarette, and a Combination of Both (Assuming Risk among Non-smokers to be Unity)

Smokers				Bidi + Cigarette Smokers					
Control group				Cancer cases		Control group			
Non-smokers	Cigarette smokers	Relative risk	$\chi^2$	Non-smokers	Bidi + cigarette smokers	Non-smokers	Bidi + cigarette smokers	Relative risk	$\chi^2$
1446	201	1.2	1.4 NS	800	54	1446	29	3.4	28.6***
1446	201	0.6	3.4 NS	249	11	1446	29	2.2	4.1*
1446	201	2.3	20.0***	140	17	1446	29	6.1	37.5***
1446	201	0.9	0.2 NS	8	—	1446	29	—	—
1446	201	0.4	1.1 NS	36	1	1446	29	1.4	0.1 NS
1446	201	1.3	1.7 NS	197	22	1446	29	5.6	39.9***
1446	201	1.0	<0.01 NS	170	3	1446	29	0.9	<0.01 NS



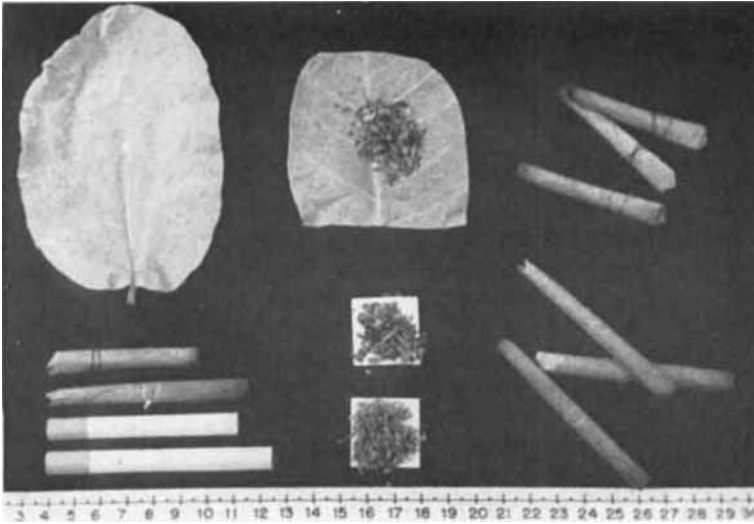


FIG. 6. Preparation of Indian bidi. *Top, left to right:* 1. leaf of temburni tree, 2. leaf cut to size + tobacco, 3. small-size bidis. *Bottom, left to right:* 1. different sizes of bidis and cigarettes, 2. cut of tobacco in bidi (*top*) and cigarette (*bottom*), 3. large-size bidis.

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