RESEARCH COMMUNICATION

A Case-control Study of Risk Factors for Lung Cancer in Mumbai, India

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Abstract

In the year 2010, it is estimated that nearly 1.35 million new cases and 1.18 million deaths with lung cancer occurred. In India, among males, lung cancer rates vary across the country which has encouraged us to conduct a case-control study to study the risk factors. The present unmatched hospital-based case-control study conducted at Tata Memorial Hospital included subjects registered between the years 1997-99. There were 408 lung 'cancer cases' and 1383 'normal controls. Data on age, tobacco habits, occupational history, dietary factors, tea, coffee were collected by the social investigators. Univariate and regression analysis were applied for obtaining the odds ratio for risk factors. In the study, cigarette smoking (OR=5.2) and bidi smoking (OR=8.3), as well as alcohol consumption (OR=1.8), demonstrated dose-response relationships with lung cancer risk. Among the dietary items, only red-meat consumption showed 2.2-fold significant excess risk. Consumption of milk showed a 60% reduction in risk; while coffee showed a 2-fold excess risk for lung cancer. In addition, exposure to use of pesticides showed a 2.5-fold significant excess risk for lung cancer.

Keywords: Lung cancer - risk factors - case-control study - tobacco - alcohol - occupation - diet - India

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Introduction

Globally, it is estimated that there are approximately 13 million new cancer cases and 8 million cancer deaths (Ferlay et al 2010). Besides the rising trend in cancer cases, some of the cancers, like lung cancer, showed remarkably high incidence rates. It is well known that lung cancer rates are high in developed countries; nonetheless, the developing countries do not lag behind and the rates are getting closer to the rates that are seen in developed countries. There is a great variation in the prevalence of lung cancer in different geographical areas. Nearly 70% of all the new cases of lung cancer in the world occur in the developed countries. Worldwide, lung cancer is the most common cancer in terms of both incidence and mortality (1.61 million new cases per year and 1.38 million deaths), with the highest rates in Europe and North America (Ferlay et al 2010).

In India, as per the estimates, there are approximately 63,000 new lung cancer cases reported each year, though the incidence (ASR per 100,000) rates are low (M=7.4, F=1.8), compared to the rates in other parts of the world (Ferlay et al 2010) . The rates of lung cancer vary across India (NCRP (2007). Lung cancer is ranked as the leading cancer in Bhopal, Chennai, Delhi, Kolkatta and Mumbai, besides north-eastern registries. As per the 2005 data available from the Indian registries, lung cancer incidence varied between 2.3 in Barshi to 14.2 in Delhi among males, and 2.6 in Barshi to 3.6 in Delhi among females (NCRP (2007) . The metropolitan cities are showing an increase in lung cancer rates over the years. In Mumbai, the rates are reported to be 9.6 in 2006 (Kurkure et al , 2010). There are many studies reporting on the risk factors for lung cancer, from India, as well from other parts of the globe (Ger et al, 1998) (Tasevska et al, 2009) .

The present study was carried out to study the risk factors for lung cancer with regard to life-style habits, diet and occupational history. This study partially funded by International Agency for Research in Cancer (IARC), and was carried out between the years 1997-99. Studies elsewhere have indicated tobacco as the major risk factor for lung cancer (Bae et al, 2007). Other risk factors reported in the literature are the asbestos, mineral exposure, radon exposure, air pollution etc. In one of the earlier studies on dietary factors, meat intake has been shown to be risk factor for lung cancer (Tasevska et al, 2009) (Freudenheim et al, 2005) (De Stefani et al, 2009). The Indian population is known to be less obese than the western population, basically attributed to the life-style. The body mass index is quite low for Indians. As per the recent survey in India , the mean BMI for Indian men (15-54 years) is 20.3 and for women (15-49 years) it is 20.5 (NFHS(2007). The Indian diet includes a major portion of vegetables and fruits. Non-vegetarian diet is rarely consumed on a daily basis, unlike in western countries. The present study thus attempts to determine the various

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factors associated with lung cancer, such as tobacco, alcohol drinking, dietary items and occupational exposure history.

Materials and Methods

The present study, a hospital-based case-control study, was conducted at the Tata Memorial Hospital (TMH), Mumbai, India. The period of data collection was 1997-99 that included subjects who visited TMH for diagnosis and treatment. Only male patients are included in the study. Patients were interviewed at the Out-patient department of TMH. The information was recorded in a pre-designed questionnaire, which was pre-tested at the hospital; this included demographic characteristics (age, sex, religion etc), life-style (habits such as smoking, chewing, alcohol drinking etc), dietary habits and occupational exposure. The hospital being a comprehensive cancer centre for diagnosis and treatment attracts patients from all parts of India. In general, in a year 30-40% of patients of total registrations are diagnosed as free of cancer. These cancer-free patients were considered as 'controls' by scrutinizing their medical history and diagnosis. Cases were microscopically proven cancer cases of lung. Controls were classified as those that were diagnosed by microscope as 'free of cancer' and not having any respiratory tract ailments and thus diagnosed as 'no evidence of disease'. During the period 1997-99, 1557 respiratory tract cancer cases were diagnosed in TMH. Of these, 408 patients with primary lung cancer, microscopically confirmed cancer cases, were considered as Cases and were interviewed for the study. Likewise, 1,383 patients who were diagnosed as 'free of cancer' and who had no respiratory tract related conditions were considered as Controls. Thus there were 408 cases of 'lung cancer' Cases and 1383 Controls that were considered as eligible entrants for this study.

The questionnaire contained socio-demographic information, life-style habits like chewing, smoking, alcohol consumption and dietary items. The questionnaire on food items were based on recollection of consumption of routine food items prior to one-year of the date of interview. Information on food frequency per week was also collected. The dietary items were classified as vegetarian diet and non-vegetarian diet. The non-vegetarian diet included items as fish, chicken and red-meat. Red-meat included mutton, liver, pork, brain etc. Consumption of vegetables, fruits, chilly was recorded. Intake of beverages as tea, coffee, milk was also recorded. Although frequency of consumption was recorded, it was not taken into account for analysis because of incompleteness.

Unconditional logistic regression model was applied for obtaining the risk estimates (odds ratio) and its 95% confidence limits using SPSS Version 15.0 software. In the analysis, independent variables were categorized into binary form and entered into the model. The results were considered for statistical significance at 5%.

Results

Demographic characteristics of Cases and Controls are shown in table-1. It is seen that the ratio of cases to controls is approximately 1: 3. The average age for cases and controls was 56.2 years and 46.5 years respectively. 75.2% and 37.7% of patients were aged more than 50 years among cases and controls respectively. Controls had a higher proportion of literates (93.3%) than cases (77.2%). Proportion of those with family history of cancer was very less in both the groups. With regard to the occupation history, it is seen that history of working in pesticides industry was more common among the cases (3.4%) , and cotton-dust workers (4.8%) among the controls.

Table 2 describes the distribution and crude odds ratio (OR) for lifestyle habits, dietary habits and occupational factors. The categories considered were 'never' vs 'ever' exposed.. It can be seen that cigarette smokers had a 2.7 times excess risk and bidi smokers had a 5.2 times excess risk, compared to the non-smokers. Tobacco chewers did not show significant risk, compared to non-chewers.

Alcohol drinkers had a 3-fold (OR=3.1), significant risk , compared to non-drinkers. With regard to the dietary items, it was noted that fish (OR=6.2), chicken (OR=6.4), red-meat (OR=6.1) , had significant excess risk for lung cancer , compared to the non-eaters of the respective food items. Consumption of vegetables didn't show any association with f lung cancer while chilly showed reduction in risk (OR = 0.3). None of the fruits, citrus or fresh fruit showed any effect on lung cancer risk.. Tea-

Table 1. Demographic Characteristics of Cases and Controls: Lung Cancer Case-control Study

Characteristics		Cases (408)		Controls (1,383)	
Age	<50	101	24.8	861	62.3
	≥50	307	75.2	522	37.7
Average			56.2		46.5
Literacy					
	Yes	315	77.2	1,290	93.3
	No	92	22.5	93	6.7
Family History					
	Yes	5	1.2	43	3.2
	No	403	98.8	1,340	99.8
Occupational history					
Pesticide worker					
	Yes	14	3.4	18	1.3
	No	393	96.4	1,365	98.7
Diesel-gas worker				96.3	
	Yes	6	1.5	25	1.8
	No	402	98.5	1,358	98.2
Paint worker				98.5	
	Yes	6	1.5	41	3.0
	No	402	98.5	1,342	97.0
Asbestos worker				98.5	
	Yes	1	0.2	1	0.1
	No	407	99.8	1,382	99.9
Metal worker				99.8	
	Yes	1	0.2	12	0.9
	No	407	99.8	1,371	99.1
Wood-dust worker				99.8	
	Yes	3	0.7	11	0.8
	No	405	99.3	1,372	99.2
Cotton-dust worker				99.3	
	Yes	8	2.0	67	4.8
	Non	400	98.0	1,316	95.2

Table 2. Odds-Ratio (crude) and 95% Confidence Interval for Life-Style Factors

Characteristics		Cases	Controls	OR 95 % CI
Cigarette Smoking	Yes	219	412	2.7 (2.2,3.4)
	No	189	971	1.0 (ref)
Bidi Smoking	Yes	153	145	5.2 (3.9,6.7)
	No	255	1,238	1.0 (ref)
Tobacco Chewing	Yes	23	103	0.7 (0.5, 1.2)
	No	385	1,280	1.0 (ref)
Alcohol Drinking	Yes	53	63	3.1 (2.1,4.6)
	No	355	1,320	1.0 (ref)
Fish Consumption	Yes	374	884	6.2 (4.3,8.9)
	No	34	499	1.0 (ref)
Chicken Consumption	Yes	373	862	6.4 (4.4,9.2)
	No	35	521	1.0 (ref)
Redmeat Consumption	Yes	366	820	6.1 (4.3,8.5)
	No	41	562	1.0 (ref)
Vegetable Consumption	No	2	8	0.8 (0.2,4.0)
	Yes	402	1,375	1.0 (ref)
Chilly Consumption	Yes	170	966	0.3 (0.2, 0.3)
	No	232	410	1.0 (ref)
Milk Consumption	Yes	286	523	0.3 (0.2, 0.3)
	No	116	855	1.0 (ref)
Tea drinking	Yes	395	1,372	4.1 (1.3,12.1)
	No	7	6	1.0 (ref)
Coffee drinking	Yes	142	212	2.9 (2.2,3.7)
	No	262	1,166	1.0 (ref)
Citrus fruit	Yes	405	1,370	0.7 (0.2 , 2.7)
	No	3	13	1.0 (ref)
Fresh fruit Consumption	Yes	406	1,376	0.3 (0.2, 4.6)
	No	2	7	1.0 (ref)
Family History	Yes	5	403	0.5 (0.2, 1.1)
	No	43	1,340	1.0 (ref)
Occupation history				
Cotton dust	Yes	8	67	0.4 (0.2, 0.8)
	No	400	1,316	1.0 (ref)
Diesel Gas	Yes	8	25	0.8 (0.3, 2.0)
	No	402	1,358	1.0 (ref)
Pesticide	Yes	14	18	2.7 (1.3, 5.5)
	No	393	1,365	1.0 (ref)

Table 2. Odds-Ratio (adjusted) and 95% Confidence Interval for Life-Style factors

Characteristics		Cases	Controls	OR 95 % CI
Cigarette Smoking	Yes	219	412	2.7 (2.2,3.4)
	No	189	971	1.0 (ref)
Bidi Smoking	Yes	153	145	5.2 (3.9,6.7)
	No	255	1,238	1.0 (ref)
Tobacco Chewing	Yes	23	103	0.7 (0.5, 1.2)
	No	385	1,280	1.0 (ref)
Alcohol Drinking	Yes	53	63	3.1 (2.1,4.6)
	No	355	1,320	1.0 (ref)
Fish Consumption	Yes	374	884	6.2 (4.3,8.9)
	No	34	499	1.0 (ref)
Chicken Consumption	Yes	373	862	6.4 (4.4,9.2)
	No	35	521	1.0 (ref)
Redmeat Consumption	Yes	366	820	6.1 (4.3,8.5)
	No	41	562	1.0 (ref)
Vegetable Consumption	No	2	8	0.8 (0.2,4.0)
	Yes	402	1,375	1.0 (ref)
Chilly Consumption	Yes	170	966	0.3 (0.2, 0.3)
	No	232	410	1.0 (ref)
Milk Consumption	Yes	286	523	0.3 (0.2, 0.3)
	No	116	855	1.0 (ref)
Tea drinking	Yes	395	1,372	4.1 (1.3,12.1)
	No	7	6	1.0 (ref)
Coffee drinking	Yes	142	212	2.9 (2.2,3.7)
	No	262	1,166	1.0 (ref)
Citrus fruit	Yes	405	1,370	0.7 (0.2 , 2.7)
	No	3	13	1.0 (ref)
Fresh fruit Consumption	Yes	406	1,376	0.3 (0.2, 4.6)
	No	2	7	1.0 (ref)
Family History	Yes	5	403	0.5 (0.2, 1.1)
	No	43	1,340	1.0 (ref)
Occupation history				
Cotton dust	Yes	8	67	0.4 (0.2, 0.8)
	No	400	1,316	1.0 (ref)
Diesel Gas	Yes	8	25	0.8 (0.3, 2.0)
	No	402	1,358	1.0 (ref)
Pesticide	Yes	14	18	2.7 (1.3, 5.5)
	No	393	1,365	1.0 (ref)

drinking (OR=4.1) and coffee-drinking(OR=2.9), showed significant risk, while milk consumption showed a 70% reduction in risk (OR= 0.3) for lung cancer. Among the occupational exposure, cotton-dust workers (OR=0.4) and pesticide workers (OR=2.7) showed association with lung cancer, while family history did not show any excess risk.

Table-3 elucidates the adjusted odds ratio, adjusted for age and literacy status, and their 95% confidence limits, for different factors under study. It is observed that after adjustment, cigarette smokers (OR=3.3) and bidi smokers (OR=3.7), continued to show enhanced risk compared to non-smokers, and alcohol drinkers (OR=3.3) too had increased risk for lung cancer compared to non-drinkers. Consumption of fish (OR=6.6), chicken (OR=6.9) and red-meat (OR=6.9) each had more than 6-fold risk for lung cancer, compared to non-eaters. Surprisingly chilli eaters continued to show reduced risk (OR=0.3). Fruit consumption, both citrus and fresh-fruit, didn't show any significant risk; among the beverages, tea-drinking showed 3-fold risk (OR=3.0) but not significant, while coffee-drinking showed 3-fold significant enhanced and milk consumption showed an 70% reduction in risk for lung cancer. Exposure to pesticide continued to show enhanced risk (OR=2.6) for lung cancer.

Table 4 demonstrates the odds ratio and confidence limits obtained by applying regression method, wherein all the factors that emerged as significant earlier were included into the regression model. Cigarette smokers showed a 5.2-fold risk and bidi-smokers 8.3-fold significant enhanced risk for lung cancer, compared to non-smokers, while tobacco-chewing didn't show any statistically significant risk. Alcohol-drinkers had 1.8-fold increase in risk, and so did the coffee-drinkers with a risk of 1.9, compared to non-drinkers. Milk consumption showed a 60% reduction in risk for lung cancer. Among the dietary items, only red meat consumption showed a 2.2-fold increase in risk, compared to non-eaters. Exposure to pesticide showed a 2.5-fold enhanced significant risk for lung cancer in our study.

Table 5 shows the dose-response relationship of the life-style habits as chewing, smoking and alcohol drinking. All the three habits showed a clear dose-response relationship with regard to the risk for lung cancer. Patients who smoked, either cigarette or bidi, for more than 30 years showed a minimum risk varying between 9.1- 9.7,

Table 4. Odds Ratio (OR) & 95% CI for Factors by regression method *

Characteristics		OR	95 % CI	
Cigarette Smoking	Yes	5.2	3.7	7.3
	No	1.0 (ref)		
Bidi Smoking	Yes	8.3	5.6	12.2
	No	1.0 (ref)		
Tobacco Chewer	Yes	0.6	0.3	1.2
	No	1.0 (ref)		
Alcohol Drinker	Yes	1.8	1.1	3.1
	No	1.0 (ref)		
Milk consumption	Yes	0.4	0.3	0.6
	No	1.0 (ref)		
Coffee Drinker	Yes	1.9	1.3	2.7
	No	1.0 (ref)		
Chicken Consumption	Yes	2.3	0.7	7.1
	No	1.0 (ref)		
Red Meat Consumption	Yes	2.2	1.0	5.1
	No	1.0 (ref)		
Fish Consumption	Yes	1.1	0.4	3.5
	No	1.0 (ref)		
Chilly Consumption	Yes	0.9	0.6	1.3
	No	1.0 (ref)		
Exposure to Pesticide	Yes	2.5	1.2	6.4
	No	1.0 (ref)		

Table 5. Dose-Response Relationship for Life-style Habits

Factor		Cases	Controls	OR	p-value
Cigarette smoking	No	189	971	1.0 (ref)	
(years)	1-10	9	89	0.5	
	11-20	36	156	1.2	< 0.00001
	21-30	77	112	3.5	
	> 30	97	55	9.1	
X2 test for Trend = 170.5					
Bidi smoking	No	255	1,238	1.0 (ref)	
	1-10	6	26	1.1	
	11-20	15	44	1.7	< 0.00001
	21-30	50	34	7.1	
	> 30	82	41	9.7	
X2 test for Trend = 214.9					
Alcohol drinking	No	355	1,320	1.0 (ref)	
	1-9	4	13	1.1	
	10-19	7	19	1.4	< 0.00001
	20-29	16	23	2.6	
	> 30	25	7	15.5	
X2 test for Trend = 56.63					

compared to the non-smokers. Similarly, those who drank alcohol for more than 30 years had an imposing 15.5 times enhanced risk, compared to non-drinkers. Test for linear trend was significant for all categories Although frequency of habit, or quantity of bidi/cigarette/alcohol consumed were collected, it was not taken into account for analysis because of incompleteness.

Discussion

Lung cancer is the most frequent cancer worldwide (Ferlay et al 2010). It is characterized by rapid development and fatal prognosis in most cases. This disease is fatal and the prognosis is poor even when diagnosed in early stage and surgically treated. The early signs and symptoms may or may not be very prominent. The incidence rates vary across the world and are highest in the developed countries. The risk factors include tobacco smoking, alcohol abuse, diet, air pollution and occupational exposure.

The present hospital-based case-control study of life-style factors, occupational exposure, dietary items, and beverages on lung cancer. There are many studies across the world studying the association of risk factors with lung cancer. In the present study, a total of 408 lung cancer cases and 1383 normal controls were analysed. Due to shortage of manpower and unforeseen circumstances, the study results could not be reported earlier. The authors wish to accept that due to the delay, there is possibility that might have been some changes in the pattern of exposure; nonetheless the study is of importance since it addresses the possible association of tobacco, dietary habits and occupational exposure to lung cancer.

Case-control studies conducted in India have shown smoking primarily as a risk factor for lung cancer. Notani and Sanghvi (1974) in their study showed a risk of 2.64 for bidi smokers. In fact, Sanghvi et al (1955) in a landmark paper were the first to show the risk of bidi smoking. The risk was more than 10-fold more for bidi smokers compared to non-smokers. The present study showed similar results, and the risk was highest for bidi smokers, which is in agreement with Sanghvi et al (1955). Smokers had an increased risk, especially bidi smokers, to the extent of 8.3-fold compared to non-smokers. Cigarette smoking also emerged as one of the strong risk factor for lung cancer, which has been demonstrated by studies from India (Notani and Sanghvi, 1974) (Sanghvi et al, 1955), as well from other parts of the world (Bae et al 2007) .

There was a clear demonstration of dose-relationship among smokers in the present study. There are many Indian studies which have implicated the role of smoking in the development of lung cancer. The risk increased dramatically for people who smoked for more than 30 years. The frequency of smoking was recorded but was not analyzed due to incompleteness. In the present study, tobacco- chewing did not show any excess risk for lung cancer.

Alcohol drinking has been shown to be a risk factor for many cancers and lung cancer was no exception, as was seen in the present study. A review study could not affirm the association strongly and had indicated for detailed studies on this aspect (Bandera et al, 2001). However, in other studies, the inferences were different (Bae et al 2007) (Freudenheim et al (2005)). Freudenheim et al (2005), in a pooled analysis using standardized exposure and covariate data from seven prospective studies with 399,767 participants and 3137 lung cancer cases showed increased risk for alcohol consumers, while Bae et al (1993) did not show any significant risk of alcohol to be associated with lung cancer. The present study showed a positive dose-response relationship for alcohol drinkers, the risk being highest (OR=15.5), for those who were drinking for more than 30 years.

Study on diet has always been difficult for various reasons. There are few studies reported from India on association of diet with lung cancer. The dietary items in the present study has been classified as vegetarians

and non-vegetarians; non-vegetarian diet included red-meat (mutton, pork), chicken, fish; vegetarian diet such as vegetables (both raw and cooked), fruits (citrus and fresh-fruit) and consumption of chilly.

Consumption of vegetables has been shown to be protective for many cancers, but the present study, did not show any association with lung cancer, but another study from New Caledonia, in the South Pacific, suggested that high consumption of dark green leafy vegetables may reduce the risk of lung cancer among men in this population (Marchand et al, 2002).

In the present study, fish and chicken eating did not show any association with lung cancer, but consumption of red-meat had a 2.2-fold excess, statistically significant, risk among the non-vegetarian dietary items, which was observed by other studies as well (Tasevska et al, 2009) (De Stefani et al, 2009).

Although tea drinking is more common in India, it did not show any additional or excess risk for lung cancer in the present study which is in agreement with an Ohsaki population-based study from Japan, where drinking green tea also did not show any association with lung cancer risk (Li et al, 2008).

Another beverage not so common as tea drinking in India, Coffee, showed almost 2-fold excess risk in our study, while another study showed risk variation between 1.31 - 1.54 for regular coffee drinkers, compared to non-drinkers (Baker et al, 2005).

Milk consumption showed a 60% reduction in risk in the present study which was in agreement with earlier study which showed reduction in risks for lung cancer (Mettlin , 1989); in this study, subjects who consumed whole milk 3 or more times daily had a 2-fold increase in lung cancer risk compared to those who reported never drinking whole milk (RR = 2.14) but the same frequency of intake of reduced-fat milk was associated with a significant protective effect (RR = 0.54).

There are several studies on various occupational exposure risk for lung cancer. Notani et al (1993) showed a 2-fold excess risk for textile workers, which could not emerge from the present study. However , use of pesticide by pesticide workers, had a direct implication on risk levels in the present study. The pesticide workers had a 2.6-fold excess risk for lung cancer , which has been demonstrated in other studies as well. In a German study, the SMR (standardized mortality ratio) of 2.0 for lung cancer morbidity (mortality) in these pesticide-exposed subjects was significantly higher than that for the general male population of the German Democratic Republic (Barthel, 1981). Prolonged exposure to the most commonly used agricultural pesticides increased the risk of lung cancer in farmers and commercial pesticide users (Dinham ,2005). A study on miners too revealed increased risk for lung cancer among smokers (Liu et al, 2008) .

Thus in the present case-control study, tobacco smoking (bidi and cigarette), alcohol drinking, consumption of red-meat and coffee drinking emerged as strong risk factors. Although tobacco and alcohol are reported as risk factors in earlier Indian studies, the present study also confirmed these findings. Tea and coffee contain catechins and flavonoids, which have been shown to exhibit anti-carcinogenic properties With regard to coffee drinking, any chemo-preventive effects of phytochemicals in coffee may be overshadowed by the elevated risk associated with caffeine in these beverages.

Milk drinking showed a 60% reduction in the present study. The possible explanation could be that a flavanone compound in milk thistle, silibinin, could be stopping the lung cancer growth. Milk thistle extract dietary supplements contains 80% of silymarin, a flavonolignan mixture and silymarin contains approximately 40% silibinin. Red-meat which contains fats, increases the cholesterol levels might have a role in increasing the risk for lung cancer for red-meat eaters. Use of pesticide by pesticide workers contributed to the enhanced risk for lung cancer in the present study. It is important to note that the participants in this study might have been exposed to higher levels for longer periods than the general population, due to their profession. The increased risk could be due to prolonged exposure to diazinon, dieldrin, metalochlor and pendimethalin, agricultural use of insecticides and herbicides

Based on this study, it may be stated that prevention of tobacco usage, periodical medical check-ups, limited usage of certain dietary items, regular consumption of milk and precautions to be taken during exposure to pesticides will prove to be more beneficial for prevention of lung cancer.

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