

Epidemiological review of laryngeal cancer: An Indian perspective

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INTRODUCTION

Laryngeal cancer is the ninth and seventh most common cause of cancer in males in Asia and India respectively. In 2012, an estimated 25,446 new case were diagnosed, and 17,560 Indians lost their lives from laryngeal cancer.^[1] In India, the incidence of laryngeal cancer has been reported to be 1.26-8.18 per 100,000 population, in different regions in the country.^[2] Epidemiological studies carried out on laryngeal cancer have highlighted the peculiarities of the disease, like varying risk factors and wide regional variation in incidence and survival. This review includes an update on the distribution of laryngeal cancer in India, as well as publication on the association between various risk factors.

MATERIALS AND METHODS

Data sources and searches

Information was gathered from a review of peer-reviewed publications on laryngeal cancer in India. MEDLINE (<http://www.pubmed.com>) and Web of science electronic

ABSTRACT

Background: Laryngeal cancer is one of the 10 leading causes of cancer in Indian men. The association of laryngeal cancer and tobacco smoking is well-established, but the peculiarities such as wide variation of disease distribution and survival, role of tobacco chewing, indoor air pollution, and dietary factors in laryngeal cancer causation needs to be understood. In this study, we review the descriptive and observational epidemiology of laryngeal cancer in India. **Materials and Methods:** MEDLINE and Web of science electronic database was searched from January 1995 to December 2013, using the using keywords “laryngeal cancer, laryngeal cancer outcome, epidemiology, etiological factor and their corresponding Mesh terms were used in combination like OR, AND.” Two authors independently selected studies published in English and conducted in India. A total of 15 studies were found to be relevant and eligible for this review. **Results:** In India, laryngeal cancer contributes to approximately 3-6% of all cancers in men. The age-adjusted incidence rate of cancer larynx in males varies widely among registries, highest is 8.18 per 100,000 in Kamrup Urban District and the lowest is 1.26 per 100,000 in Nagaland. The 5-year survival for laryngeal cancer in India is approximately 28%. Indian studies show tobacco, alcohol, long-term exposure to indoor air pollution, spicy food, and nonvegetarian diet as risk factors for laryngeal cancer. **Conclusion:** There is wide regional variation in the incidence of laryngeal cancer in India. Survival rates of laryngeal carcinoma are much lower as compared to other Asian countries. Studies conducted in India to identify important risk factors of laryngeal cancer are very limited, especially on diet and indoor air pollution. Hence, more research is required for identifying the etiological factors and development of scientifically sound laryngeal cancer prevention programs.

Key words: *Epidemiology, etiological factor, laryngeal cancer*

database was searched from January 1995 to December 2013, using the using keywords such as “laryngeal cancer, treatment, clinical characteristics, laryngeal cancer outcome, epidemiology, etiological factor and their corresponding Mesh terms were used in combination like OR, AND.” We also examined bibliographies of included articles to identify additional references. The search strategy was limited to English language. Only journal article type was included. Figure 1 presents the search strategy and screening process.

Study selection

Inclusion criteria

1. Study designs eligible for inclusion in our review were randomized controlled trials, nonrandomized controlled trails, cohort studies and cross-sectional studies conducted to assess the disease distribution, its

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risk factors, survival, and any other factors affecting epidemiology of laryngeal cancer.

- Studies conducted in India only were included in the review.

Exclusion criteria

- Studies not conducted in India were excluded from the review.

Data extraction and analysis

The title and abstract of each citation were screened first, and full report was screened next, if necessary, to select the relevant articles according to selection the criteria. Full texts of these selected studies were retrieved, reviewed and extracted for relevant data by authors independently. A total of 15 studies were included in the review and their findings presented. The descriptive statistical data for laryngeal cancer were mainly obtained from publications of the Indian Cancer Registry, UICC, International Agency for Research on Cancer (IARC) and WHO (GLOBOCON-2012).

Descriptive epidemiology

The Indian cancer registries include 25 Population Based Cancer Registries (PBCR) and 07 Hospital Based Cancer Registries (HBCR), of the 25 PBCR's, 11 PBCR's are urban, 02 are rural and remaining 12 correspond to urban and rural both by virtue of being state or district registries.^[2] The data obtained from these Indian Cancer Registries indicates that in India cancer larynx is far more common in males as compared to females. Laryngeal cancer contributes to approximately 3-6% of all cancer in males and only about 0.2-1% of all cancers in females.^[2]

The age-adjusted incidence rate of cancer larynx in males was found to vary widely among registries, highest being 8.18 per 100,000 in Kamrup Urban District and the lowest being 1.26 per 100,000 in Nagaland followed by 1.55 per 100,000 in Barshi rural. Most of the registries in western and central India have an age-adjusted incidence rate of cancer larynx between 3.5 and 5 per 100,000 population. However, certain older, cancer registries such as Delhi and Bhopal have reported a higher age-adjusted incidence rate of 7.61 and 6.43 per 100,000 respectively^[2] [Table 1]. This wide variation of age-adjusted incidence rate among registries need to be interpreted cautiously as many registries are newly established and it has been demonstrated that in their initial years of operation, registries might include prevalent cases or may also miss certain cases till they are well established. Similar to global trends of cancer larynx, Delhi and Mumbai registries have also shown a statistically significant decreasing trend over the past 25 years. However, the Bhopal registry reported a statistically significant increasing trend of cancer larynx^[3] [Table 2].

More than 50% of patients in both males and females were older than 60 years. The maximum numbers of cases were reported in the age group of 60-69 years amounting to 31.93% of all larynx carcinoma in males and 27.29% in females^[2] [Table 3]. Data from HBCR show that almost 70% of all female cases and 50% of male cases were either illiterate or had primary level education^[4] [Table 4]. Data from HBCR also indicate that almost 80% of both male and female cases had regional diseases at the time of presentation^[5] [Table 5].

The 5-year survival rate for cancer larynx in India is approximately 28%.^[6] This indicates that prognosis from cancer larynx remains poor as compared to other Asian countries such as China, South Korea, and Singapore [Table 6]. A wide variation of survival rates is also observed between rural and urban India. This could be because Indian registries suffer with the problem of under-reporting of death, which is more pronounced in the rural area. In addition, the lack of health infrastructure in rural India results in lower survival rates as compared to urban areas. The 5-year age-standardized relative survival of laryngeal cancer for different Indian registries and its comparison with other Asian registries is shown in Table 6.^[6,7]

Risk factors

Tobacco

The most important risk factor for cancer larynx appears to be the tobacco use. National Cancer Registry Program enlists laryngeal cancer as one of the tobacco-related cancer.^[8] The IARC monograph also classifies tobacco use as a carcinogenic to humans based on overwhelming on epidemiological evidence.^[9] A large number of case-control

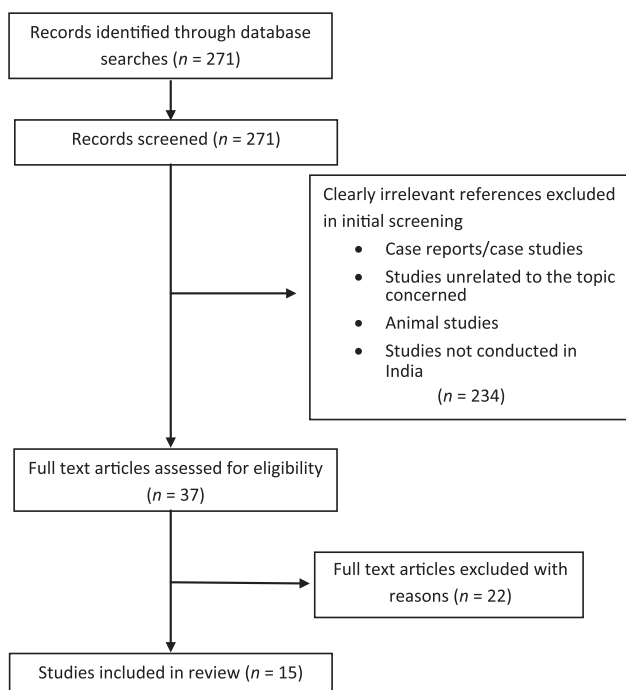


Figure 1: Summary of evidence search and selection

Table 1: Age-adjusted (world) incidence and mortality rates of larynx cancer* and its relative proportion in Indian PBCR

Registry	Males			Females		
	Relative proportion* (%)	Incidence (AAR) [#]	Mortality (AAR)	Relative proportion* (%)	Incidence (AAR) [#]	Mortality (AAR)
Bengaluru (2008-2009)	3.12	3.72	0.90	0.32	0.47	0.10
Barshi rural (2009-2010)	3.66	1.55	0.40	0.66	0.52	0.30
Bhopal (2009-2010)	5.38	6.43	1.50	0.62	0.76	0.20
Chennai (2009)	3.78	4.58	1.00	0.29	0.37	—
Delhi (2008-2009)	5.50	7.61	0.80	0.77	0.99	0.10
Mumbai (2009-2010)	4.63	4.79	2.10	0.61	0.66	0.30
Cachar district (2009-2010)	5.07	6.47	2.20	1.27	1.25	0.30
Dibrugarh district (2009-2011)	3.20	3.44	0.80	0.38	0.30	—
Kamrup urban district (2009-2011)	4.15	8.18	3.40	0.63	0.97	0.40
Manipur state (2009-2010)	2.73	2.35	0.20	0.74	0.64	0.10
Mizoram state (2009-2010)	2.76	5.32	1.30	0.45	0.72	0.50
Sikkim state (2009-2011)	3.67	3.33	1.00	0.51	0.48	0.50
Ahemdabad rural (2009-2010)	3.92	3.31	0.60	0.28	0.14	—
Ahemdabad urban (2009-2010)	3.73	4.77	0.80	0.58	0.58	0.10
Aurangabad (2009-2010)	6.35	4.49	0.50	0.56	0.38	—
Kolkata (2008-2009)	5.36	4.94	2.00	0.77	0.75	0.30
Kollam (2009-2010)	3.79	4.59	1.90	0.22	0.20	0.10
Nagpur (2008-2009)	5.96	6.36	1.10	0.53	0.59	0.20
Pune (2009-2010)	5.91	4.81	1.60	0.75	0.56	0.40
Thiruvananthapuram (2009-2011)	4.31	5.86	2.00	0.45	0.59	0.10
Meghalaya state (2010-2011)	4.80	7.86	2.20	0.70	0.62	0.20
Tripura (2010)	6.66	5.27	1.20	1.02	0.54	—
Nagaland (2010)	1.83	1.26	—	0.91	1.21	—
Wardha (2010-2011)	2.76	1.74	0.90	0.73	0.41	0.30

*ICD10-C32; *Proportion of larynx cancer out of total cancer cases observed; [#]AAR – Age-adjusted rate per 100,000; PBCR – Population Based Cancer Registries

Table 2: The age-adjusted (world) incidence rates and APC for larynx cancer in males in Indian PBCR during the years 1982-2009

Registry	AAR*	APC
Bengaluru	3.83	-0.41 ^s
Bhopal [¶]	4.72	2.93 [#]
Chennai	4.51	0.24 ^s
Delhi [¶]	8.34	-0.72 [#]
Mumbai	6.61	-1.84 [#]

*AAR – Average age-adjusted rate per 100,000; [#]Significant at 0.05;

^sNonsignificant; [¶]The AAR and AAPC are for the years 1988-2009.

APC – Annual percentage change; AAPC – Average annual percentage change; PBCR – Population Based Cancer Registries

and cohort studies conducted in various parts of the world have observed many fold increase in cancer larynx with the use of various forms of tobacco.^[10-12]

In India, tobacco is both chewed and smoked in several forms. A common form of smoking tobacco is “bidi” an Indian cigarette, containing 0.2-0.3 g of tobacco rolled in a dried leaf, usually temburni leaf (*Diospyros mylanoxylon*). The other types of smoking in India are described by Sanghvi *et al.*^[13] Many studies on laryngeal cancer in India implicated smoking as a risk factor. The risk level varied from 1.5-fold to 7-fold for different forms of tobacco

smoking. In one of the earlier studies, Rao *et al.*^[14] found that bidi and cigarette smoking to be associated with cancer of the larynx, however, the risk of laryngeal cancer was found to be much more for bidi than for cigarette. Other subsequent case-control studies also found bidi and cigarette smoking to be significantly associated with laryngeal carcinoma.^[15-17] A cohort study of 65,553 men aged 30-84 in Karunagappally Taluk, Kerala also found that laryngeal cancer was strongly related to bidi and cigarette smoking as well as the number smoked per day ($P < 0.001$) and duration of smoking ($P < 0.001$), bidi smoking was found to have higher risk than cigarette smoking [Table 7].^[18]

Chewing of tobacco in the form of khaini, zarda, mawa, pan, etc. is also prevalent in India. Many studies including a large multicentric case-control study of 511 laryngeal cancer cases have not found tobacco chewing as a risk factor for laryngeal carcinoma.^[14-16,18,19] However, Kapil *et al.* in a hospital-based case-control study consisting of 305 laryngeal cancer patients found chewing of betel leaf with tobacco to increase the risk for laryngeal cancer by 2.37-fold but like other studies it failed to find any association between cancer larynx and tobacco chewing.

Table 3: Age-wise distribution of larynx cancer

Age range (years)	Number of male (%)	Number of female (%)
15-19	5 (0.16)	3 (0.78)
20-24	6 (0.19)	4 (1.04)
25-29	11 (0.36)	4 (1.04)
30-34	22 (0.71)	13 (3.38)
35-39	83 (2.69)	13 (3.38)
40-44	151 (4.89)	24 (6.23)
45-49	264 (8.56)	39 (10.13)
50-54	443 (14.36)	46 (11.95)
55-59	421 (13.65)	38 (9.87)
60-64	534 (17.31)	63 (16.36)
65-69	451 (14.62)	44 (11.43)
70-74	329 (10.66)	41 (10.65)
75+	365 (11.83)	53 (13.77)

Data from 25 PBCR NCRP report 2009-2011. NCRP – National Cancer Registry Program; PBCR – Population Based Cancer Registries

Table 4: Distribution of larynx cancer as per educational status

Education	Male (percentage of cases)	Female (percentage of cases)
Illiterate	23.89	49.50
Literate	6.46	5.98
Primary	19.49	15.28
Middle	16.96	11.63
Secondary	22.42	11.30
College	10.77	6.31

Data from 7 HBCR (Bengaluru, Bhopal, Chennai, Chandigarh, Dibrugarh, Guwahati, Mumbai and Trivanthapuram), NCRP report 2007-2011. HBCR – Hospital Based Cancer Registries; NCRP – National Cancer Registry Program

Table 5: Clinical extent of the disease (larynx cancer) at presentation

Clinical extent of disease	Male (percentage of cases)	Female (percentage of cases)
Localized	19.38	17.31
Regional	78.21	79.51
Distant	2.41	3.28

Data from 7 HBCR (Bengaluru, Bhopal, Chennai, Chandigarh, Dibrugarh, Guwahati, Mumbai and Trivanthapuram), NCRP report 2007-2011. HBCR – Hospital Based Cancer Registries; NCRP – National Cancer Registry Program

Alcohol

Besides tobacco use, alcohol consumption has also been implicated as a risk factor in the development of laryngeal carcinoma. There is a dearth of Indian studies on the association between alcohol and laryngeal cancer, mainly due to social stigma associated with the alcohol habit and ban on alcohol drinking in certain states of India. Furthermore, women in India do not openly admit to the habit of alcohol consumption.^[14] However, a few case-control studies and one cohort study found an almost 2-4-fold increase in risk of laryngeal cancer due to alcohol consumption [Table 7].^[14-16] These studies, provide evidence of alcohol as an additional risk factor for laryngeal carcinoma, which is in conformity with several western studies.^[10-12,20,21]

Table 6: 5-year age standardized (0-74 years) relative survival for laryngeal cancer in selected Indian populations and selected Asian countries

Population/country	Years	Relative survival (%) (range)
Mumbai*	1990-2001	36
Chennai*	1990-2001	38
Bhopal*	1990-2001	15.7
Barshi*	1990-2001	15.7
Karunagappally*	1990-2001	28.3
India (over-all)*	1990-2001	28 (16-38)
China*	1990-2001	68 (49-73)
Singapore*	1990-2001	66
Turkey*	1990-2001	71
South Korea*	1990-2001	62 (59-76)
Thailand*	1990-2001	36 (26-49)

Source: *Reference (Survcan); *Reference (Shankar)

Indoor air pollution

International Agency for Research on Cancer monograph on indoor air pollution classifies indoor air pollution from coal usage as a known human carcinogen (IARC Group 1), while that from biomass (primarily wood) as a probable human carcinogen (IARC Group 2A).^[22,23] In a developing country like India where as much as 74% of the total population uses solid fuels for cooking,^[24] it has been estimated that indoor air pollution may account for up to 4-6% of the national burden of disease.^[25] A multicentric case-control study conducted in India between 2001 and 2004, found no increased risk of laryngeal cancer among ever-users of solid fuels compared to lifelong users of modern fuel. However, long duration (>50 years) of coal usage was found to be a risk with duration-dependent increase in risk for laryngeal cancer^[26] [Table 8]. One of the major limitations of this study was low proportion of female study participants (male 478, female 33), as women in India spend a greater proportion of their time indoors performing various cooking related activities, the intensity of exposure is likely to be higher among women compared with men. Considering that, this was the only study in India which has tried to assess indoor air pollution as a risk factor for laryngeal carcinoma, it would be worthwhile to plan a study with larger proportion of female participants to explore the differential risk between males and females.

Dietary factors

Data on the nutritional factors associated with cancer of the larynx is limited. A hospital-based case-control study consisting of 305 laryngeal cancer patients conducted during 2000-2002, assessed the role of dietary items such as fruits, vegetables, egg, meat, and spicy food.^[15] The study reported that there was an inverse association between the risk of laryngeal cancer and consumption of roots and

Table 7: Association between tobacco and carcinoma larynx

Risk factor	Study period	OR (95% CI)	Sample size (case/control)	Study design and place
Tobacco smoking				
Never	1980-1984	1	1062 (427/635)	Case-control, Mumbai ^[14]
Bidi		2.30 (1.7-3.2)		
Cigarette		1.50 (0.9-2.4)		
Bidi and cigarette		1.5 (0.4-6.0)		
Nonsmoker	2000-2002	1	610 (305/305)	Case-control, New Delhi ^[15]
Smoker		4.54 (3.15-6.56)		
Never	2001-2004	1	1229 (511/718)	Case-control, multicenteric ^[16]
Cigarette		5.74 (3.20-10.31)		
Bidi		5.32 (3.18-8.90)		
Bidi and cigarette		5.42 (2.37-12.39)		
Nonsmoker	2001-2004	1	417 (217/200)	Case-control, Kolkata ^[17]
Smoker		1.75 (0.89-3.44)		
Never	1990-2005	1 [#]	65,553* (cases - 85)	Cohort, South India ^[18]
Bidi		5.5 [#] (2.8-10.8)		
Cigarette		1.7 [#] (1.1-2.7)		
Tobacco chewing				
Nonuser	1980-1984	1	1062 (427/635)	Case-control, Mumbai ^[14]
Pan-tobacco		1.1 (0.82-1.47)		
Nonusers	2000-2002	1	610 (305/305)	Case-control, New Delhi ^[15]
Users		1.09 (0.66-1.79)		
Betel leaf with tobacco		2.37 (1.12-5.06)		
Never	2001-2004	1	1229 (511/718)	Case-control, multicenteric ^[16]
Khaini		1.06 (0.39-2.90)		
Zarda		0.36 (0.04-3.07)		
Mawa		0.98 (0.26-3.75)		
Pan		1.06 (0.43-2.62)		
Gutkha		2.55 (0.62-10.44)		
Nonusers	1990-2005	1 [#]	65,553* (cases-85)	Cohort, South India ^[18]
Users		0.9 (0.6-1.5) [#]		
Alcohol				
Nondrinker	1980-1984	1	1062 (427/635)	Case-control, Mumbai ^[14]
Drinker		1.68 (1.20-2.43)		
Nondrinker	2000-2002	1	610 (305/305)	Case-control, New Delhi ^[15]
Drinker		3.98 (2.66-5.94)		
Nondrinker	1990-2005	1 [#]	65,553* (cases-85)	Cohort, South India ^[18]
Drinker		2.1 [#] (1.3-3.5)		

*Cohort study; [#]RR – Relative risk; CI – Confidence interval; OR – Odds ratio

tubers, vegetables, and fruits. The risk of laryngeal cancer was found to be 5.25, 5.67, and 3.28 times higher for those who consumed roots and tubers, green leafy vegetables and fruits <4 times per week.^[13] A 2-3-fold increase in risk of laryngeal cancer was also observed with consumption of eggs, meat, and spicy food. However, Rao *et al.* in his case-control study of 427 subjects failed to find any association between nonvegetarian diet and laryngeal cancer.^[14] An earlier study (Notani and Jayant, 1987) reported the similar inverse relationship between laryngeal cancer and consumption of fruit and vegetables.^[27] Several Western studies also reported reduced laryngeal cancer risk with consumption of fruits and vegetables.^[28-30] The studies on diet and laryngeal cancer though few, provide a window

of opportunity to study further the role of vegetarian diet in the prevention of laryngeal cancer.

Prevention

It is very evident from the large number of studies conducted across the globe that tobacco and alcohol are perhaps important risk factors for laryngeal cancer. The risk rises with increasing levels of smoking and alcohol drinking, each agent approximately multiplying the effects of the other.^[31,32] Thus, studies conducted to examine the effect of stopping smoking, drinking or both have demonstrated that the risk laryngeal cancer appears to decline steeply with time, by over 70% in 10 or more years after stopping smoking,^[33-35] however the similar clear pattern with stoppage of drinking has not been

Table 8: Association between indoor air pollution and carcinoma larynx (OR by type and duration of fuel usage)

Risk factor	Study period	OR ^{ab} (95% CI)	P _{trend}	Sample size (case/control)	Study design and place
Modern fuel usage	2001-2004	1		1229 (511/718)	Case-control, multicentric ^[26]
Wood usage (>0-30 years)		0.72 (0.43-1.22)	0.88		
Wood usage (>30-50 years)		0.99 (0.65-1.52)			
Wood usage (>50 years)		0.95 (0.63-1.43)			
Coal usage (>0-30 years)		0.47 (0.10-2.30)	0.05		
Coal usage (>30-50 years)		1.33 (0.52-3.40)			
Coal usage (>50 years)		3.65 (1.11-11.93)			

^aAdjusted for centre, age sex, SES (education, family income, crowdedness) and cumulative tobacco consumption; ^bAdditionally adjusted for alcohol years, chewing tobacco product and snuffing. SES – Socioeconomic status; OR – Odds ratio; CI – Confidence interval

demonstrated.^[35-37] These effects of smoking and drinking cessation are from western studies, and similar studies have not been done in India. Indians have one of the most interesting diets, with many unique dietary constituents that have promise for cancer prevention. A few epidemiological studies exploring the relationships between diet, lifestyle and cancer have been carried out in India, but none in respect of diet and prevention of laryngeal carcinoma.

Opinions are divided about screening for cancer in the early stage and for hyperplastic alterations of the laryngeal mucosa. No screening trails for laryngeal cancer have been conducted in India. The few trails conducted in western population considering availability, the time and effort required for the conduct of screening test, have not recommended screening for laryngeal cancer.^[38]

CONCLUSIONS

Laryngeal cancer has a varying distribution in India. Some regions report a decreasing while others report an increasing trend. Indian studies have well-established tobacco smoking and alcohol as major risk factors for laryngeal carcinoma. Studies from India exploring the role of factors such as diet and indoor air pollution are limited. There is a need to conduct well-designed studies to understand the etiology of laryngeal cancer and implement preventive programs.

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Conflicts of interest

There are no conflicts of interest.

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Important Meeting dates in 2014-2015

Meeting	Venue	Contact
7 th UAE Cancer congress, 29 th -31 st Oct	Dubai	uaecancercongress@mci-group.com
APNETS, 30-31 st Oct	Penang, Malaysia	admin@apnets.org
Haematocon, 5 th -8 th Nov	Bangalore	info@haematocon2015.com
Biennial Joint Conference of ISMPO & ISO, 6 th -8 th Nov	Mumbai	ismpoiso2015@gmail.com
2 nd Brinker Awardee Breast Cancer Symposium, 14 th /15 th Nov	Bangalore	Bhawna.sirohi13@gmail.com
1 st Breast Cancer Year in Review Conference, 16 th /17 th Jan 2016	Mumbai	yir.breastcancer@gmail.com