Review Article

Lung Cancer in India–Part I

D. Behera

Emritus Professior and Ex-Dean, Postgraduate Institute of Medical Education and Research, Chandigarh, and President, Indian Society for Study of Lung Cancer, India

This article is available on www.vpci.org.in

ARTICLE INFO

Received: May 17, 2021

Accepted: June 14, 2021

Indian J Chest Dis Allied Sci 2021;63:143-192

KEY WORDS

Lung cancer, India, Cancer Registry, Epidemiology, Histology, Dignosis, Management

ABBRIVATIONS USED IN THIS ARTICLE

PBCRs=Population Based Cancer Registries

DALYs =Disability-adjusted life-years

GBD=Global burden of disease

NCDs=Non-communicable diseases

GLOBOCAN=Global Cancer Incidence, Mortality and Prevalence

IARC=International Agency for Research on Cancer

WHO=World Health Organization

LMICs=Lower and Middle Income Countries

ASRs=Age-standardised rates

SEER=Surveillance, Epidemiology, and End Results

NSCLC=Non-small-cell lung cancer

SCLC=Small cell lung cancer

cont... page 194

Abstract

Lung cancer in India has changed over the years. The subject was reviewed earlier in 2004. Since then, it has become an important and second common cancer in Indian males. Although smoking continued to be an important factor for the causation of lung cancer in this country, particularly *bidi* smoking, new facts come into light. Biomass fuel is another important factor in the causation of lung cancer in non-smoking females. There is also a regional disparity in the prevalence of lung cancer in India. Aizawl district had the highest rank in incidence rates in both males (38.8 per 100,000) and females (37.9 per 100,000). There was a significant increase in the incidence rates of lung cancer in Kamrup (urban), Chennai, Delhi and Bangalore PBCRs (Population Based Cancer Registries) in both males and females. Five PBCRs showed a significant increase in incidence rates among males whereas it was seen in 11 PBCRs among females. In Asia, among males, Yueyanglou (95.5 per 100,000) in China had the highest incidence rate of lung cancer, whereas Aizawl district (37.9 per 100,000), had the highest age adjusted ratio in females. Over the years, there is also marked improvement in the availability of diagnostic facilities all over the country. There is also a significant transition of the cell type of lung cancer. While earlier reports showed squamous cell type as the commonest one, now adenocarcinoma has surpassed that as reported from most centers in the country including the National Cancer Registry maintained by the Indian Council of Medical Research. Advent of molecular biology is a new development since we reviewed the topic nearly 16 years back. This aspect has been discussed in detail in the second part of the review. However, lung cancer continues to present in a very advanced stage of the disease where definite therapy, like surgery could not be offered to most of them. In fact around 3% to 4% of cases could only be offered surgery in our country. There is a significant improvement in the management of advanced stage lung cancer with the availability of newer chemotherapeutic drugs and targeted therapy and immunotherapy (will be discussed in 2nd part) with better median survival and many centers in the country are now treating this disease more aggressively. Although smoking continues to be a major problem in India, more and more anti-tobacco laws are being persued aggressively by the Government. Lung cancer screening is not yet practised in our country because of various technical, and other logistic issues. COVID-19 pandemic has created difficulties in managing such patients.

Corresponding author: Dr D Behera, Director, Pulmonary Medicine, Fortis Health Care, Mohali, Punjab, 160062; E-mail:dirlrsi@gmail.com

Introduction

Lung cancer was considered to be rare in earlier years in the world as well as in India.[1-3] However, over the years, the incidence is gradually increasing with profound changes in its epidemiology, pathology, diagnostic modalities and availabilities of various therapeutic modalities, although there may be some differences in certain countries. We had reviewed the problem of lung cancer in India in 2004[4] and over the past 16 years, tremendous advances and numerous developments have taken place with more and better improvements in our understanding of the disease. The most significant advances that have taken place are in the field of molecular biology of lung cancer, particularly in the knowledge of mutations and genetic variations in lung cancer with the availability of targeted therapies with an improved survival by many folds. Immuno-oncology and its applicability in lung cancer with further improvements in survival is another area of advanced development in managing the disease. Further, in our country there is a change in the epidemiological pattern of the disease that will be discussed in detail in this review.

The Global Scenario

Global health has steadily improved over the past 30 years, as measured by the age-standardised disability-adjusted life-years (DALYs). However, the recent estimates of incidence, prevalence, mortality, and DALYs due to 369 diseases and injuries, for two sexes, and for 204 countries and territories by the Global Burden of Disease (GBD) surveys revealed that lung cancer which was the fifth common cause of DALYs lost in 1990 that was 3.6% (3.3% – 3.9%) of the total, is now 3.9% (3.4% – 4.3%), although still continues to be the fifth position in 2019 for ages between 50-74 years in both the sexes.[5] This is a 64.3 (48.8 – 80.2) percentage change in number of DALYs between 1990–2019. For 75 years and above, the DALYs was 1.9% in 1990 (10th position) and the same is 2.6% (7th position) in 2019 with a change of 164.3% between these years. The percent change in age-standardised DALYs rate between 1990–2019 was -19.8 for ages between 50-74 years and for ages above 74 years and above this was 16.4%.[5] Currently non-communicable diseases (NCDs) in general and cancer in particular are responsible for most of the global morbidity and mortality[6] and cancer is expected to be the leading cause of death and will be an important barrier to increase life expectancy in every country of the world in the 21st Century. It is the second commonest cause of death (16%) following cardiovascular diseases (31%)[7,8] with an alarming increase in the rate and mortality world over. The Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) that reports the global cancer incidence, mortality and prevalence database is an initiative of International Agency for Research on Cancer (IARC) and is a dedicated cancer organisation of the World Health Organization (WHO). The GLOBOCAN 2018 estimated the Global Cancer Statistics for 2018 that included the incidence and mortality worldwide for 36 cancers in 185 Countries.[9] Nearly 18.1 million new cancer cases were estimated to occur in 2018 and 9.6 million cancer patients died in that year. By 2040, these figures will be more than one and a half times to about 29.4 million every year with the number of cancer-related deaths of 16.4 million, with the greatest increase in LMICs (Lower and Middle Income Countries), where more than two-thirds of the world's cancers will occur. Cancer is the cause of about 30% of all premature deaths from NCDs among adults aged 30-69 years.[10] Lung cancer was the most common form of cancer in both sexes combined (11.6% of the total cases) and was the leading cause of cancer death (18.4% of the total cancer deaths), followed by female breast cancer (11.6%), prostate cancer (7.1%), and colorectal cancer (6.1%) for incidence and colorectal cancer (9.2%), stomach cancer (8.2%), and liver cancer (8.2%) for mortality. Among males, lung cancer was the most frequent cancer and the leading cause of cancer death and prostate and colorectal cancer (for incidence) and liver and stomach cancer (for mortality) followed this. In females, breast cancer was the most common and was also the leading cause of cancer death, followed by colorectal and lung cancer (for incidence), and *vice versa* (for mortality). The most frequently diagnosed cancer and the leading cause of cancer death, however, substantially vary across countries and within each county depending on the degree of economic development and associated social and life style factors although high-quality cancer registry data, the basis for planning and implementing evidence-based cancer control programmes use, are not available in most LMICs. The distribution of incident cases and deaths for the 10 most common cancers are shown in table 1 and figure 1.[9]

The GLOBOCAN 2018 data reveal substantial global diversity in leading cancer types, particularly for incidence in men (10 different cancer types) and mortality in both men (9 types) and women (6 types). Prostate cancer is the most frequently diagnosed cancer in 105 countries, followed by lung cancer in 37 countries, and liver cancer in 13 countries. Lung cancer is the leading cause of cancer death among men in 93 countries, in part because of its high fatality rate, followed by prostate cancer (46 countries) and liver cancer (20 countries). In women, the profile of the most commonly diagnosed cancers across countries is marked

Table 1. Global incident cases and deaths for some important cancers and all cancers combined in 2018[9]

Site of Cancer	Number of New Cases (% of all sites)	Number of Deaths (% of all sites)
Lung	2,093,876 (11.6)	1,761,007 (18.4)
Breast	2,088,849 (11.6)	626,679 (6.6)
Prostate	1,276,106 (7.1)	358,989 (3.8)
Colon	1,096,601 (6.1)	551,269 (5.8)
Non-melanoma of skin	1,042,056 (5.8)	65,155 (0.7)
Stomach	1,033,701 (5.7)	782,685 (8.2)
Liver	841,080 (4.7)	781,631 (8.2)
Rectum	704,376 (3.9)	310,394 (3.2)
Oesophagus	572,034 (3.2)	508,585 (5.3)
Cervix uteri	569,847 (3.2)	311,365 (3.3)

by its dichotomous nature, with female breast cancer most frequent in terms of new cases in the majority (154 countries) of countries and with cervical cancer leading in most (28 of 31 countries) of the remaining countries. The mortality profile among women is more heterogeneous, with breast and cervical cancer as the leading causes of cancer death in 103 and 42 countries, respectively, followed by lung cancer in 28 countries. The incidence and mortality rates vary 20-fold between the regions. The variation is similarly large across countries. The highest incidence rates among men are in Europe, particularly in Eastern European countries, such as Hungary (77 cases per 100,000 in males) as well as Western Asia, (particularly in the former Soviet Union) and in certain countries in Asia, such as Turkey and China. Among women, lung cancer incidence rates are highest in Hungary (38 cases per 100,000 in females), followed by other European countries, Northern America, Australia, and New Zealand. In general, the geographic patterns of lung cancer mortality are quite similar to those of incidence due to the relatively poor prognosis of the disease after diagnosis. Historically, lung cancer mortality rates have been higher among males than females due to an earlier uptake of smoking in large numbers. More recently, reports have noted a convergence in incidence and mortality rates between young men and women in Europe, North America, and Australia, due to a larger decrease in rates in men and a substantial rise (or slower decline) in women who acquired the smoking habit later than men. In Asia, Latin America, and Africa, however, the lung cancer burden among men still largely exceeds that of women at all ages. In the last few decades, mortality rates among men in these regions have started to decline, however, with rates among women often remaining low.[11]

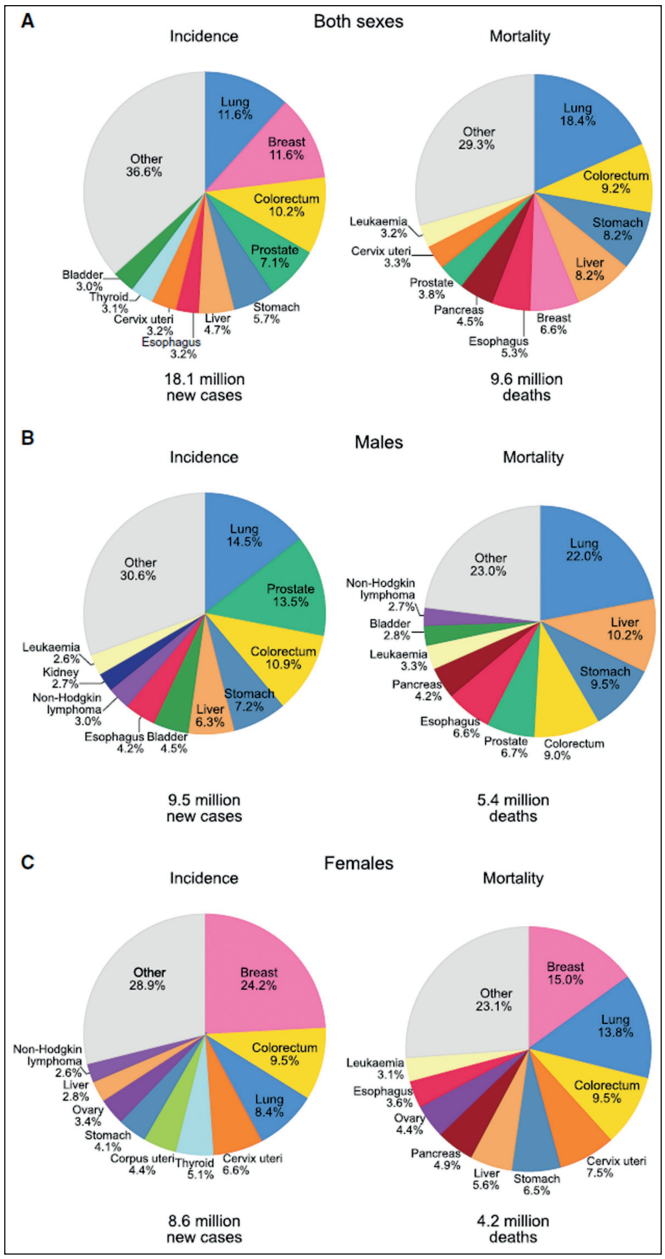

Figure 1. Distribution of cases and deaths for the 10 most common cancers in the world in 2018 for (A) both sexes, (B) males, and (C) females. For each sex, the area of the Pie-chart reflects the proportion of the total number of cases or deaths; non-melanoma skin cancers are included in the "other" category.

Source: GLOBOCAN 2018[9]

Thus, as it will be seen from the above description, lung cancer remains the leading cause of cancer incidence and mortality worldwide, with 2.1 million new lung cancer cases and 1.8 million deaths in 2018, representing close to 1 in 5 (18.4%) cancer deaths. Among males, lung cancer is the leading cause of death in most countries in Eastern Europe, Western

Asia (notably in the former Soviet Union), Northern Africa, and specific countries in Eastern Asia (China) and South-Eastern Asia (*e.g.*, Myanmar, the Philippines, and Indonesia). The highest incidence rates among men are observed in Micronesia/Polynesia, in Eastern Asia (rates are above 40 per 100,000 in China, Japan, and the Republic of Korea), and in most of Europe, especially in Eastern Europe, with an age-standardised rates (ASRs) in Hungary as high as 77.4 per 100,000 males (Figure 2).

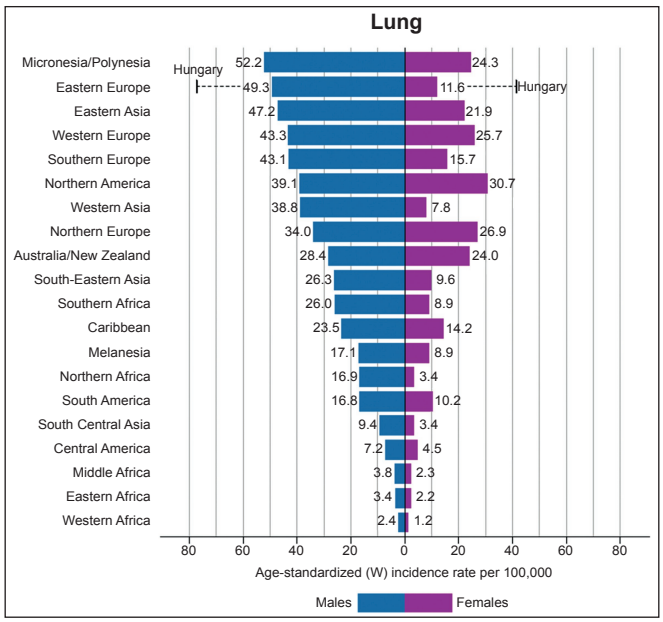

Figure 2. Region-specific incidence of age-standardised rates by sex for lung cancers in 2018. Rates are shown in descending order of the world (W) age-standardised rate among men, and the highest national rates among men and women are superimposed.

Source: GLOBOCAN 2018[9]

Incidence rates among males remain generally low in Africa, although these range from intermediate to high in several countries in both Northern and Southern regions, notably in Morocco (31.9 per 100,000) and South Africa (28.2 per 100,000). Among females, lung cancer is the leading cause of cancer deaths in 28 countries. The highest incidence rates are seen in North America, Northern and Western Europe (notably in Denmark and the Netherlands), and Australia/New Zealand, with Hungary topping the list. It is of note that the incidence rates among Chinese women (22.8 per 100,000) are not dissimilar to those observed among females in several Western European countries like France [22.5 per 100,000], despite substantial differences in smoking prevalence between the two populations. The high lung cancer incidence rates in Chinese women, despite their low smoking prevalence, are thought to reflect increased exposures to smoke from burning of charcoal for heating and cooking.

The 20-fold variation in lung cancer rates by region largely reflects the maturity of the tobacco epidemic and differentials in the historic patterns of tobacco exposure, including intensity and duration of smoking, type of cigarettes, and degree of inhalation. Among men, a diminution in smoking prevalence, followed by a peak and decline in lung cancer rates in the same generations, was first observed in several high-income countries where smoking was first established, including the United Kingdom, the United States, Finland, Australia, New Zealand, the Netherlands, Singapore, and (more recently) Germany, Uruguay, and the remaining Nordic countries. A recent analysis of incidence trends in 26 European countries revealed that rates in men aged 35 to 64 years have been decreasing in recent years, including Eastern European countries, although rates were still increasing in Bulgaria. Among women, the epidemic is less advanced and, in contrast to men, most countries are still observing a rising trend in incidence, and only a relatively few populations (*e.g.*, the United States [whites] and possibly the United Kingdom) are showing signs of a peak and decline among recent birth cohorts. Given the differential trends by sex, rates in men and women are converging in several European countries, and it is postulated that this is the result of sex-specific differences in the distribution of histologic subtypes as well as smoking prevalence. In the United States, lung cancer incidence rates are now higher among young women than among young men, with the pattern confined to non-Hispanic whites and Hispanics; intriguingly, a sex-specific difference in smoking behaviour is not considered a likely explanatory factor. In countries where the epidemic is at an earlier stage, surveillance data are more limited. In China and Indonesia, smoking has either peaked or continues to increase and, in several African countries, lung cancer rates are likely to continue to increase at least for the next few decades, barring interventions to accelerate smoking cessation or reduce initiation. In India, *bidi* smoking confers a risk close to that of cigarette smoking, yet no significant changes in lung cancer incidence rates (*i.e.*, among males, in whom prevalence is high) have been observed in either sex, at least in the urban areas with long-standing and robust incidence data (Figure 3). With greater than 80% of lung cancers in Western populations attributed to smoking, the disease largely can be prevented through tobacco control. Best-practice measures that effectively reduce active smoking and prevent involuntary exposure to tobacco smoke—particularly increasing excise taxes and prices on tobacco products, as well as implementing plain packaging and graphic health warnings on tobacco products and enforcing comprehensive bans on tobacco advertising—are embedded in the WHO

Framework Convention on Tobacco Control and, after its adoption in 2003, 168 signatories have ratified the agreement. According to the Continuous Update Project of the World Cancer Research Fund and the American Institute of Cancer Research, that analyses the research on cancer prevention and survival, lung cancer was the most common cancer worldwide in 2018. Figure 3 shows the country-wise ranking of lung cancer. Hungary had the highest rate of lung cancer in 2018, followed by Serbia in combined both sexes as well as in men; and while Hungary had the highest rate in females, Denmark followed it.

GLOBOCAN 2020

The IARC released the updated GLOBOCAN 2020 on December 14, 2020 with new estimates on the global cancer burden, indicating that it has risen to 19.3 million cases and 10 million cancer deaths in 2020.[12] The data provides an update on the global cancer burden using the GLOBOCAN 2020 estimates of cancer incidence and mortality produced by the IARC. Worldwide, an estimated 19.3 million new cancer cases (18.1 million excluding non-melanoma skin cancer) and almost 10.0 million cancer deaths (9.9 million excluding non-melanoma skin cancer) occurred in 2020. Female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million (11.7%), new cases followed by lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%) cancers. Lung cancer remained the leading cause of cancer death, with an estimated 1.8 million (18%) deaths, followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers. Overall incidence was from 2-fold to 3-fold higher in transitioned *versus* transitioning countries for both sexes, whereas mortality varied <2-fold for men and little for women. Death rates for female breast and cervical cancers, however, were considerably higher in transitioning *versus* transitioned

Both Sexes

Rank	Country	ASR
1	Hungary	56.7
2	Serbia	49.8
3	New Caledonia (France)	42.3
4	Greece	40.5
5	French Polynesia	39.8
6	Montenegro	39.7
7	Belgium	39.0
8	Guam	37.9
9	Turkey	36.9
10	Denmark	36.6
11	Poland	36.5
12	North Korea	36.2
13=	Bosnia & Herzegovina	36.1
13=	France (metropolitan)	36.1
15	Samoa	35.4
16=	China	35.1
16=	US	35.1
18	Macedonia	34.1
19=	Germany	33.7
19=	Ireland	33.7
21	Netherlands	33.3
22	Slovenia	32.9
23	Croatia	32.5
24	UK	32.5
25	Slovakia	31.2

Men

Rank	Country	ASR
1	Hungary	77.4
2	Serbia	71.6
3	Turkey	70.6
4	Greece	67.8
5	Montenegro	62.9
6	Bosnia & Herzegovina	62.4
7	New Caledonia (France)	59.9
8	Armenia	58.5
9=	French Polynesia	55.7
9=	Macedonia	55.7
11	Belarus	54.5
12	Slovakia	54.3
13	Guam	53.7
14	Poland	52.7
15	Lithuania	52.6
16	Belgium	52.2
17	Latvia	51.8
18	Estonia	51.4
19	France (metropolitan)	51.3
20	Croatia	50.9
21	Romania	50.7
22	Moldova	50.5
23	Bulgaria	50.1
24	Russia	48.2
25	North Korea	48.1

Women

Rank	Country	ASR
1	Hungary	41.4
2	Denmark	36.3
3	Netherlands	32.7
4	Iceland	32.5
5	Serbia	30.9
6	US	30.8
7	UK	30.2
8	Canada	29.3
9=	Ireland	29.2
9=	Norway	28.1
11	Belgium	28.0
12	Samoa	27.4
13=	Germany	27.4
13=	North Korea	27.4
15	Brunel	26.6
16	New Zealand	26.4
17	New Caledonia (France)	26.0
18	Poland	24.5
19	Guam	24.3
20	Cuba	24.1
21	Australia	23.6
22	French Polynesia	23.4
23	Austria	23.3
24	China	22.8
25	France (metropolitan)	22.5

Figure 3. Lung cancer age-standardised rates per 100,000 population in the world.

Souce: GLOBOCAN 2018[9]

countries (15.0 *versus* 12.8 per 100,000 and 12.4 *versus* 5.2 per 100,000, respectively). The GBD is expected to be 28.4 million cases in 2040, a 47% rise from 2020, with a larger increase in transitioning (64% to 95%) *versus* transitioned (32% to 56%) countries due to demographic changes, although this may be further exacerbated by increasing the risk factors associated with globalisation and a growing economy.

With an estimated 2.2 million new lung cancer cases and 1.8 million deaths, this is the second most frequently diagnosed cancer and the leading cause of cancer death in 2020, representing approximately one in 10 (11.4%) cancers diagnosed and one in 5 (18.0%) deaths (Figure 4). Lung cancer is the leading cause of cancer morbidity and mortality in men, whereas, in women, it ranks third for incidence, after breast and colorectal cancer, and second for mortality, after breast cancer. Incidence and mortality rates are roughly two times higher in men than in women, although the male-to-female ratio varies widely across the regions, ranging from 1.2 in Northern America to 5.6 in Northern Africa. Lung cancer incidence and mortality rates are 3 to 4 times higher in transitioned countries than in transitioning countries; this pattern may well change as the tobacco epidemic evolves given that 80% of smokers aged ≥15 years resided in LMICs in 2016. Among men, lung cancer is the most commonly diagnosed cancer in 36 countries, while it is the leading cause of cancer death in 93 countries. The highest incidence rates are observed in Micronesia/Polynesia, Eastern and Southern Europe, Eastern Asia, and Western Asia, where Turkey has the highest rate among men globally (Figure 5). Incidence rates remain generally low in Africa, although these range from intermediate to high in both Southern and Northern regions.

Among women, lung cancer is the leading cause of cancer death in 25 countries in Northern America, Oceania, and parts of Europe (Figure 6). The highest incidence rates are in Northern America, Northern and Western Europe, Micronesia/Polynesia, and Australia/New Zealand, with Hungary having the highest country-specific rates (Figure 5). Rates are also high in Eastern Asia, largely reflecting the high burden among Chinese women, which is thought to reflect high outdoor ambient air pollution and exposures to other inhalable agents, such as household burning of solid fuels for heating and cooking given their low smoking prevalence. The global proportion of lung cancer deaths attributable to outdoor ambient $PM_{2.5}$ (*fine particulate matter*) air pollution was 14% in 2017, ranging from 4.7% in the United States to 20.5% in China. International variation in lung cancer rates and trends largely reflects the maturity of the tobacco epidemic, with patterns in

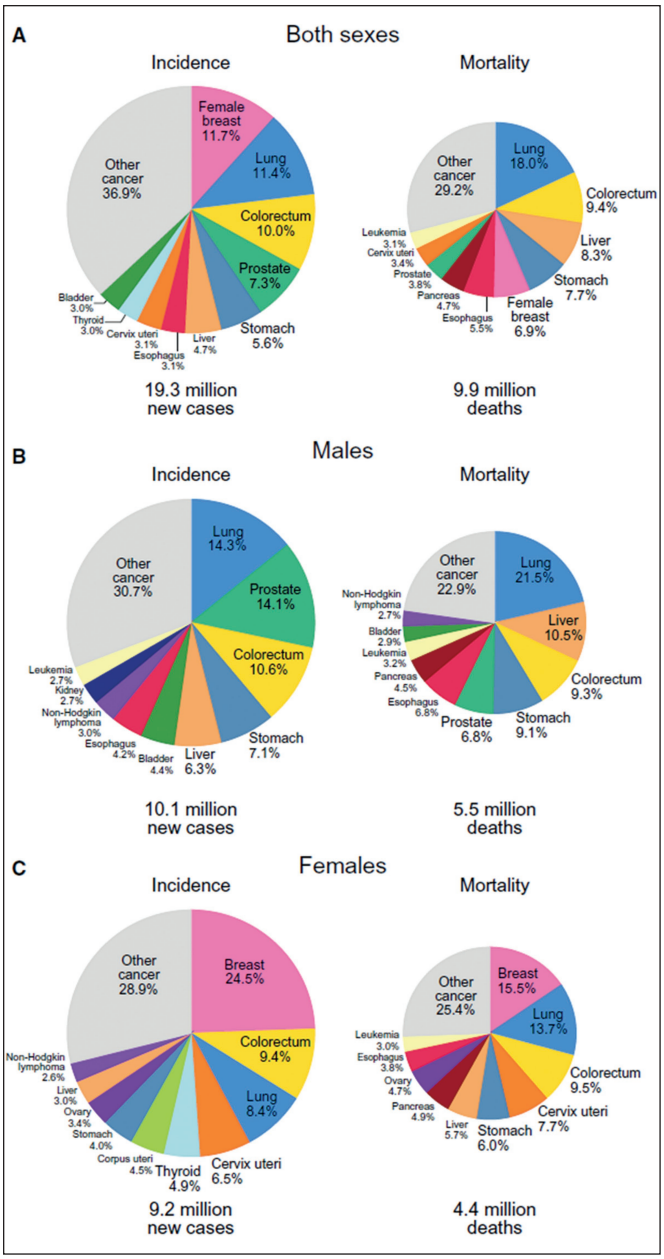

Figure 4. Distribution of cases and deaths for the top 10 most common cancers in 2020 for (A) both sexes, (B) males, and (C) females. For each sex, the area of the Pie-chart reflects the proportion of the total number of cases or deaths; non-melanoma skin cancers (excluding basal cell carcinoma for incidence) are included in the "other" category.

Source: GLOBOCAN 2020[12]

mortality paralleling those in incidence because of the high fatality rate. Smoking was first established among men in several high-income countries, including the United Kingdom, the United States, Finland, Australia, New Zealand, the Netherlands, Singapore, and, more recently, Germany, Uruguay, and the remaining Nordic countries and was followed by a steep increase in lung

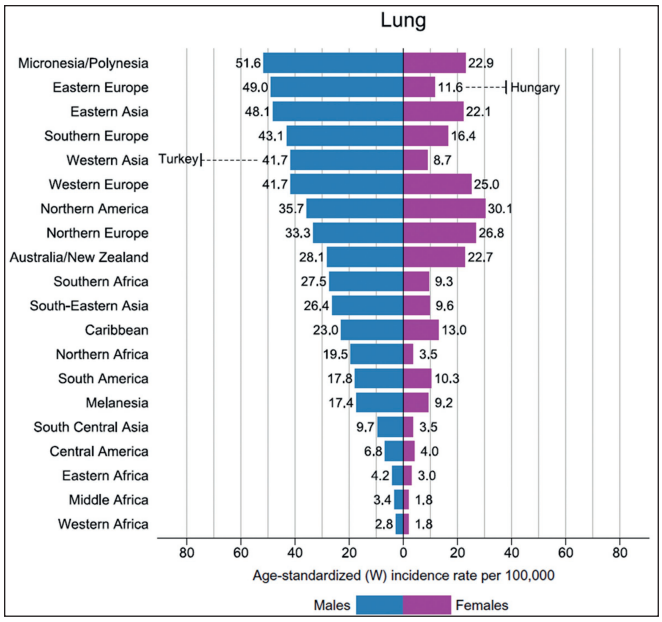

Figure 5. Region-specific incidence age-standardised rates for lung cancer by sex among males and females in 2020. Rates are shown in descending order of the world (W) age-standardised rate in men, and the highest national rates among men and women are superimposed.

Source: GLOBOCAN 2020[12]

cancer. Subsequent declines in lung cancer followed peak smoking prevalence by several decades and were first observed in young birth cohorts. In contrast, among women, the tobacco epidemic is less advanced and defined, and most countries are still observing a rising incidence of lung cancer. Only a relatively few populations, *e.g.*, the United States and Switzerland, show signs of a peak and stabilisation or decline, *albeit* at a slower pace compared with those in men. As a result of this sex-specific trend, incidence rates among women are approaching or equalling those among men in several countries in Europe and Northern America. From 2006 to 2008, female incidence rates were even higher than male incidence (ages 35-64 years) in Denmark, Iceland, and Sweden. More recent studies revealed a higher female-to-male incidence ratio in successively younger birth cohorts in the United States and subsequently in more countries, including Canada, Denmark, Germany, New Zealand, the Netherlands, because of increasing incidence rates among women in contrast to steep declines among men. The increasing female-to-male incidence ratio, however, was not fully explained by sex-specific differences in smoking behaviour. In countries where the epidemic is at an earlier stage, including China, Indonesia, and several African countries, smoking has either peaked recently or continues to increase, hence, lung cancer rates will likely increase for at least the next few decades barring interventions to accelerate smoking cessation or reduce initiation. With about two-thirds of lung cancer deaths worldwide attributable to smoking, the disease can be largely prevented through effective tobacco-control policies and regulations.

USA

The American Cancer Society estimates about 228,820 new cases of lung cancer (116,300 in men and 112,520 in women) in the United States for 2020 and about 135,720 deaths will occur from lung cancer (72,500 in men and 63,220 in women). The most common cancers in descending order are breast cancer, lung and bronchus cancer, prostate cancer, colon and rectum cancer, melanoma of the skin, bladder cancer, non-Hodgkin lymphoma, kidney and renal pelvis cancer, endometrial cancer, leukaemia, pancreatic cancer, thyroid cancer, and liver cancer (Table 2).

Table 2. Estimated new cases and death due to lung cancer in 2020 in USA (SEER data)

Rank	Common Types of Cancer	Estimated New Cases 2020	Estimated Deaths 2020
1.	Breast cancer (Female)	276,480	42,170
2.	Lung and bronchus cancer	228,820	135,720
3.	Prostate cancer	191,930	33,330
4.	Colorectal cancer	147,950	53,200
5.	Melanoma of the skin	100,350	6,850
6.	Bladder cancer	81,400	17,980
7.	Non-Hodgkin's lymphoma	77,240	19,940
8.	Kidney and renal pelvis cancer	73,750	14,830
9.	Uterine cancer	65,620	12,590
10.	Leukaemia	60,530	23,100

Prostate, lung, and colorectal cancers will account for an estimated 43% of all cancers diagnosed in men in 2020. For women, the three most common cancers will be breast, lung, and colorectal, and these account for an estimated 50% of all new cancer diagnoses in women in 2020.[13] Lung cancer mainly occurs in older people. Most people diagnosed with lung cancer are 65 or older; a very small number of people diagnosed are younger than 45 years. The average age of people when diagnosed is about 70 years. Lung cancer is by far the leading cause of cancer death among both men and women, making up almost 25% of all cancer deaths. Each year, more people die of lung cancer than of colon, breast, and prostate cancers combined. On a positive

note, the number of new lung cancer cases continues to decrease, partly because people are quitting smoking. Also, the number of deaths from lung cancer continues to drop due to people stopping smoking and advances in early detection and treatment. There are population-based differences in the outcome and presentation of lung cancer patients based upon racial, histologic, and economic factors.[14]

The variation was further observed from other studies. Using the Surveillance, Epidemiology, and End Results (SEER) data, the clinical and epidemiological pattern of patients with lung cancer revealed that from 1973 to 2015, the average incidence of lung cancer was 59/100,000 person. The incidence increased initially, reached a peak in 1992, and then gradually decreased. A higher incidence rate was observed in males than in females and in blacks than in other racial groups in USA. Since 1985, adenocarcinoma became the most prevalent histopathological type. The surgical rate for lung cancer was about 25%, and treatment with chemotherapy showed an increasing trend, while the radiotherapy rate was in downward trend. The surgical rate for non-small-cell lung cancer (NSCLC) was higher than that for small cell lung cancer (SCLC), while chemotherapy for SCLC far exceeded that for NSCLC. Treatment with chemotherapy and radiotherapy for advanced stage had higher rate than early stage. The 5-year relative survival rate of lung cancer increased with time, but was but <21%.[15] The updated data for 2020 is given in figure 6 and the estimates for 2021 are shown in table 3.[16]

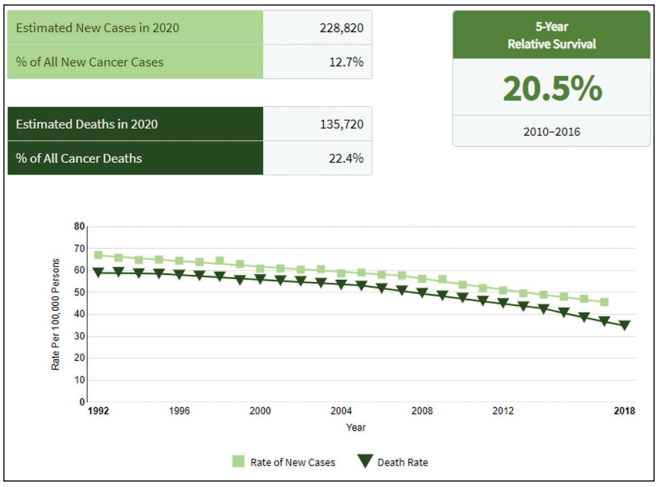

Figure 6. Cancer Stat Facts: Lung and bronchus cancer in USA over the years.

Source: Surveillance, Epidemiology, and End Results (SEER) 18 registries, National Cancer Institute, 2020

Europe

In Europe, there were an estimated 3.91 million new cases of cancer (excluding non-melanoma skin cancer) and 1.93 million deaths from cancer in 2018. The most common cancer sites were cancers of the female breast (523,000 cases), followed by colorectal (500,000), lung (470,000) and prostate cancer (450,000). These four cancers represent half of the overall burden of cancer in Europe. The most common causes of death from cancer were cancers of the lung (388,000 deaths), colorectal (243,000), breast (138,000) and pancreatic cancer (128,000). In the European Union (EU)-28, the estimated number of new cases of cancer was approximately 1.6 million in males and 1.4 million in females, with 790,000 men and 620,000 women dying from the disease in the same year. The estimates are based on the recorded data from 145 PBCRs in Europe.[17,18] As per the data released to the European Cancer Information System (ECIS) that measures the cancer burden and its time trends across Europe, the cancer burden is estimated to have risen to 2.7 million new cases (all types, excluding non-melanoma skin cancer) and 1.3 million deaths in 2020. Lung cancer was the second most common cancer in men (14.2%) and third most common cancer in women (9.1%). The estimated incidence and mortality by country is shown in figure 7.[19]

Table 3. Cancer statistics for USA (Lung and Bronchus), estimates for 2021

Estimated New Cases in 2021			Estimated Deaths in 2021		
Males	Females	Total	Males	Females	Total
119,100	116660	235,760	69,410	62,470	131,880
Incidence rates 2013–2017	58.4	Average annual rate per 100,000, age adjusted to the 2000 US standard population			
Death rates 2014–2018		Average annual rate per 100,000, age adjusted to the 2000 US standard population. Rates for PR are for 2012–2016			

Source: American Cancer Society, 2021

Asia-Pacific Region

Earlier studies about a decade old[20] has shown that cancer is becoming an increasingly important health problem in the low-and middle-income countries in the Asia-Pacific region, as well as in high-income countries because of ageing populations and changes in life-style associated with economic development and epidemiologic transition (data was limited to East Asia, South Eastern Asia and Pacific Islands countries, territories and other areas), with relevant information primarily extracted from the GLOBOCAN 2008, Cancer Incidence in Five Continents series and WHO websites. Most LMICs have a cancer control strategy and/or an action plan; however, coverage of cancer

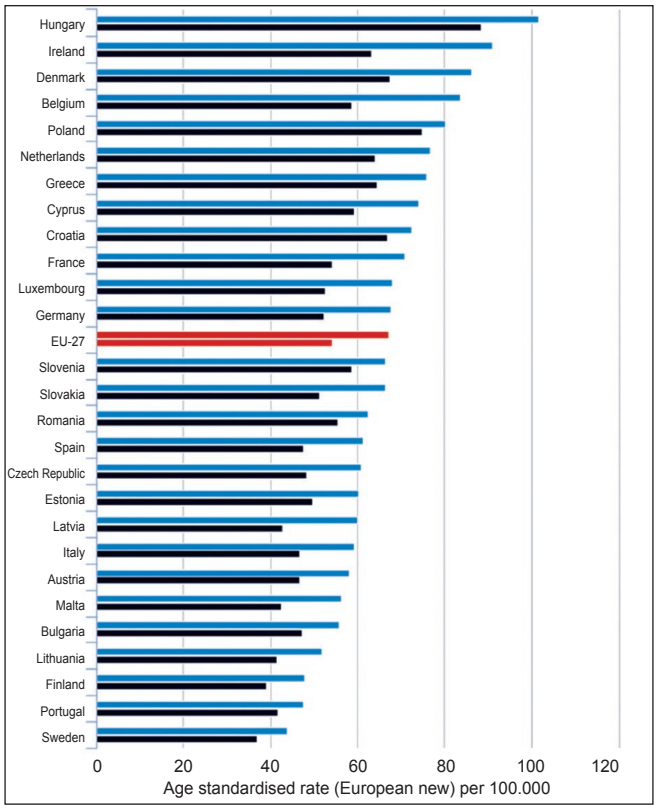

Figure 7. Estimated incidence and mortality by countries in Europe for 2020.

Source: European Cancer Information System-2020.

registration is still very low and does not meet the international standard in terms of quality. Therefore, only limited data were available for the recent global estimation of cancer burden. Large variations, in both cancer incidence and mortality, were observed in the populations in the different sub-regions of Asia. The most common cancer in males is lung cancer in the Eastern and South Eastern sub-regions, while prostate cancer comes close to lung cancer in the Pacific Island countries. In females, breast cancer is the most common in all three regions. The predominance of lung, stomach, colorectal, prostate, breast and cervical cancers makes cancer control more amenable in the Asia-Pacific region. Up-to-date statistics on cancer occurrence and outcome are essential for the planning and evaluation of cancer control programmes. Priority can be given to population-based cancer registration, risk reduction, especially tobacco control, and primary health-care based enhancement of health-care systems to diagnose and manage cancer specifically in LMICs. Lung cancer continued to be a major form of cancer in Japan.[21] Of the five most common cancers in Japan, lung cancer is the second common in both sexes combined and also in men following colorectal cancer and third in women following breast cancer and colorectal cancer.[22]

Cancer is still a major health problem in China and lung cancer remains the most common type of cancer diagnosed, and was attributed to nearly 30% of all cancer-related deaths. The incidence of the five most common cancers, in China, in 2015, including cancers of the lungs, stomach, colorectum, liver and breast, accounted for almost 60% of all cancers diagnosed.[23] Cancer statistics in China were updated by the National Central Cancer Registry on the basis of data from 368 qualified cancer registries. It was estimated that the total number of newly diagnosed cases of lung cancer in the People's Republic of China in 2015 was about 787,000, corresponding to over 2100 new lung cancer diagnoses each day. Lung cancer accounted for about 20% of all cancer diagnoses, and the age-standardised incidence rate by world standard population was estimated to be 35.92 per 100,000 in the country in 2015. The age-standardised incidence rates of lung cancer for male and female populations were 48.87 and 23.52 per 100,000, respectively, which represented 520,300 male and 266,700 female individuals diagnosed each year. The urban areas had a lower age-standardised incidence rate for lung cancer for the male population than the rural areas, whereas the opposite was true for the female population (24.17 and 22.61 per 100,000 in urban areas and in rural areas, respectively). The age-specific lung cancer incidence rate was relatively low below the age of 40 and increased dramatically after that, reaching a peak in the age group of 80 to 84 years, both in male and female populations. Before then, the incidence rates were significantly lower in female individuals than in male individuals. It was estimated that about 630,500 patients with lung cancer died in 2015, which is equivalent to an average of over 1700 deaths each day. Lung cancer accounted for 27% of the mortality of all sites combined, and the age-standardised mortality rate was estimated to be 28.02 per 100,000 in the People's Republic of China in 2015. The numbers of lung cancer deaths were 433,200 and 197,300, with age-standardised rates for lung cancer mortality of 40.11 and 16.54 per 100,000 for the male and female populations, respectively. The rural areas had relatively higher age-standardised rates of lung cancer mortality (40.41 per 100,000) for male individuals than the urban areas (39.85 per 100,000). The trend for lung cancer mortality in different age groups was similar to the trend for incidence.[24]

India

Lung cancer was considered to be rare in earlier reports till in the late fifties and early sixties, when various research studies were available in Indian literature.[3] Publications on lung cancer started appearing from all parts of the country as described later. The topic

was reviewed by us and others[4,25-31] wherein different aspects of the disease have been discussed. Further authentic data is available from the National Cancer Registry Programme of the Indian Council of Medical Research (ICMR) which is a reliable source repository of data for surveillance of cancer in the country through its 36 Population-based Cancer Registries (PBCRs) and 236 Hospital-based Cancer Registries (HBCRs) established over a period of 38 years since 1982. The other sources of information are the GLOBOCAN 2018[9] and 2020[12] and the GBD study. Detailed clinical experience and information is also available from different parts of the country by various researchers and authors.

The Report of the National Cancer Registry Programme (NCRP), 2020 released on 18th August 2020 by the ICMR, provides reliable cancer data in the country between 2012 and 2016. As mentioned above, initiated in 1982, it has now 36 PBCRs and 236 HBCRs. The current report incorporates data from 28 PBCRs and 58 HBCRs.[32] Delhi PBCR covered the largest population person years of 17.3 million and the lowest was covered by Pasighat PBCR in Arunachal Pradesh with 0.13 million population person years. The highest age-adjusted ratios (AARs), was recorded per one lakh population for all sites of cancer combined was for Aizawl district (269.4) among males and Papumpare district of Andhra Pradesh (219.8) had among females. One in four persons had a chance of developing cancer in Papumpare district of Andhra Pradesh in their lifetime in the age group 0-74 years. The 58 HBCRs registered a total of 667,666 cases of cancer during this period. HBCR at Tata Memorial Hospital registered the highest (81260) number of cases. A rise in the incidence of all sites of cancer was observed in majority of the PBCRs. In India, the total number of incidence cases of cancer in males is estimated to be 679,421 in 2020 and 763,575 in 2025. Among females, the total number of incidence cases is estimated to be 712,758 in 2020 and 806,218 in 2025. Cancer breast (238908) is expected to be the most common site of cancer in 2025 followed by cancer lung (111,328) and mouth (90,060). Tobacco-related cancers are estimated to constitute 27% of all cancers in India.

Cancer incidence and its pattern among all the PBCRs for all sites of cancer across 28 PBCRs showed that Aizawl district (38.8), Mizoram state (32.1) and Kollam district (23.1) had higher AARs than any other PBCR in males and in females, the three areas of Aizawl district (37.9), Mizoram state (27.6) and Imphal West district (16.6) were at the top followed by Papumpare district of Andhra Pradesh (12.8) (Figure 8).

Lung cancer was the leading and commonest form amongst males in 9 of the 28 PBCRs (Delhi, Kolam, Tiruvanantpuram, Bengaluru, Chennai, Kolkata, Mumbai, Manipur, Tripura); second commonest in six sites (Patiala, Hyderabad, Aurangabad, Wardha, Bhopal, Pasighat); and third in six sites (Ahmedabad, Pune, Nagpur, Mizoram, Sikkim, Cachar). Thus, lung cancer was the commonest form of malignancy in males in India during this period (2012-2016). Amongst females, it was the second commonest form in Manipur and Mizoram. North-East registries had higher incidence rates of lung cancer than the other registries. A significant increase in the incidence rates of cancer lung was observed in 5 PBCRs and 11 PBCRs in males and females, respectively. Aizawl district had the highest incidence of lung cancer in Asia among females. Systemic therapy was the most common mode of treatment both in males and females. In Asia, Aizawl district, India (37.9) had the highest AAR per one lakh among females. Over the years, the incidence of lung cancer has shown a change in its trend when compared between 1982-91 and 2006-2015. Lung cancer remained in the same position as the leading site in both the periods in Delhi, and similarly, lung cancer continued to be the top leading site across the years in Mumbai. In Bangalore, stomach cancer was the top leading site of cancer followed by lung in the period 1982-1991, whereas the order interchanged in the period 2005-2014. In Chennai, stomach was the leading site of cancer in the period 1988-1991 and lung cancer was the second leading site. However, both stomach and lung cancer continued to be at the top but exchanged the top two positions in 2007-2016. Lung was the most common site of cancer associated with use of tobacco in the males in the East (33.8%), North (31.0%), and South (26.1%) regions. In females, cancer oesophagus and cancer lung had the highest proportion among the cancers associated with use of tobacco in north (32.3%).

The number of cases registered for cancer lung and its relative proportion to all sites of cancer (%), crude, AARs and truncated incidence rates per 100,000 populations and its rank in 28 PBCRs under the registry programme is shown in table 3. Crude incidence rate refers to the rate obtained by division of the total number of cancer cases by the corresponding estimated population (mid-year) and multiplying by 100,000; age adjusted or AARs cancer incidence increases as age increases. Therefore, higher the proportion of older population, higher is the number of cancers. Most developed and western countries have a higher proportion of older population. So in order to make rates of cancer comparable between countries, a world standard population that takes this into account is used to arrive at age adjusted or age standardised rates. This is calculated according to the direct method of Boyle and Parkin, 1991 by obtaining the age specific rates and applying these rates to the standard population in

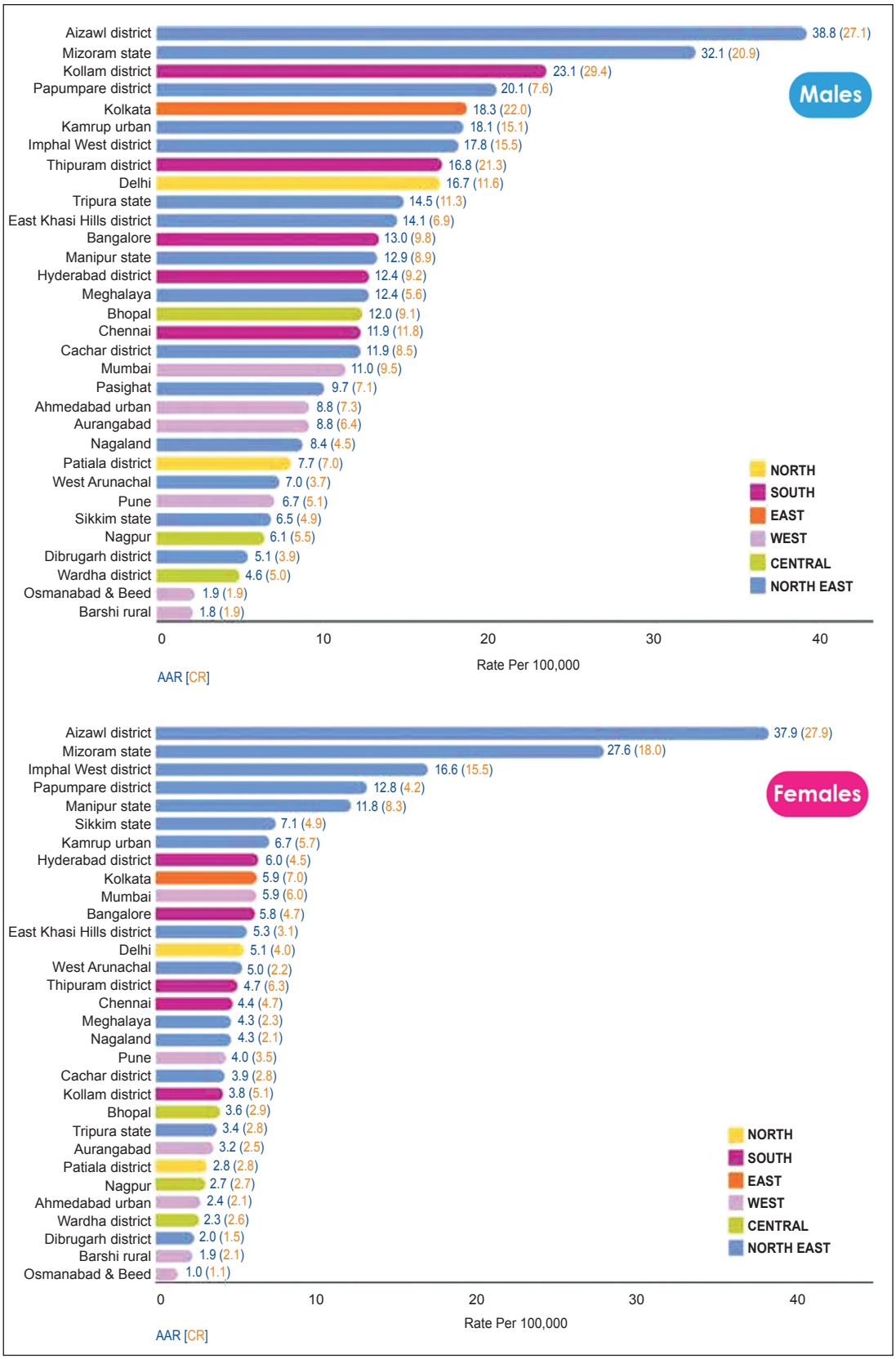

Figure 8. Comparison of age adjusted incidence rates of 28 PBCRs under National Cancer Registry Programme of the Indian Council of Medical Research.

Reproduced with permission from: NCRP, ICMR (Open Source)

that age group; truncated age adjusted incidence rate, this is similar to the except that it is calculated for the truncated age group 35-64 years of age). Aizawl district had the highest rank in incidence rates in both males (38.8 per 100,000) and females (37.9 per 100,000).

There was a significant increase in the incidence rates of cancer lung in Kamrup urban, Chennai, Delhi and Bangalore PBCRs in both males and females. Five PBCRs showed a significant increase in incidence rates among males whereas it was seen in 11 PBCRs among females (Figure 9). GLOBOCAN 2018 data for 2018 for India is shown in table 4 and figures 10-13.[9,33]

Data of GLOBOCAN-2018 and 2020 for India are presented in table 5 and figures 8-13.[9,33] Breast cancer is the most frequently observed cancer (14% of the total cases) and it is the leading cause of cancer death (11.1% of the total cases) in India in both the sexes in 2018 (table 4 and figures 8-11). In terms of incidence, breast cancer is followed by cancers of lip oral cavity (10.4%), cervix uteri (8.4%), lung (5.9%), and stomach (5%). Cancers of breast, lip oral cavity, and cervix uteri are responsible for more than 32% of the total cancer burden. For mortality, breast cancer is followed by cancers of lip, oral cavity (9.3%), lung (8.1%), cervix uteri (7.7%), and stomach (6.6%).[5,7] Figures 10 and 11 shows the distribution of estimated number of new cases and deaths (both sexes combined) in 2018 in India.[9,32] Cancers of lip, oral cavity are the leading cause of cancer incidence (16.1%) and mortality (12.3%) in males. This is followed by cancers of lung (8.5%), stomach (6.8%), colorectal (6.4%), and oesophagus (5.9%). Leading causes of cancer mortality included lung (11%), stomach (8.5%), oesophagus (7.6%), and colorectum (6.9%) in males.[9] Among females, breast cancer is the commonest (27.7%) followed by the cancers of cervix uteri (16.5%), ovary (6.2%), lip oral cavity (4.8%), and colorectum (3.4%). Breast cancer is also the leading cause of cancer death in women (23.5%) followed by cancers of cervix uteri (16.2%), ovary (6.5%), lip, oral cavity (5.9), and lung cancer (74.9%)[9] indicating that lung cancer is an important problem in India.

GLOBOCAN 2018 has estimated over 1.1 million new cases and 0.78 million cancer deaths in India in 2018.[9] Table 6 shows the distribution of number of new cases and deaths for the first 10 common cancer types. Lung cancer is the fourth common cancer type; however, if the sex specific sites are excluded, like breast and cervix, then it is the second common cancer type.

Some more and unique information on lung cancer is available from the recently published comprehensive picture of the patterns and time trends of the burden of total cancer and specific cancer types in each state of India estimated as part of the GBD. Injuries, and Risk Factors Study (GBD) 2016 and such a systematic compilation was not readily available.[34] The group used

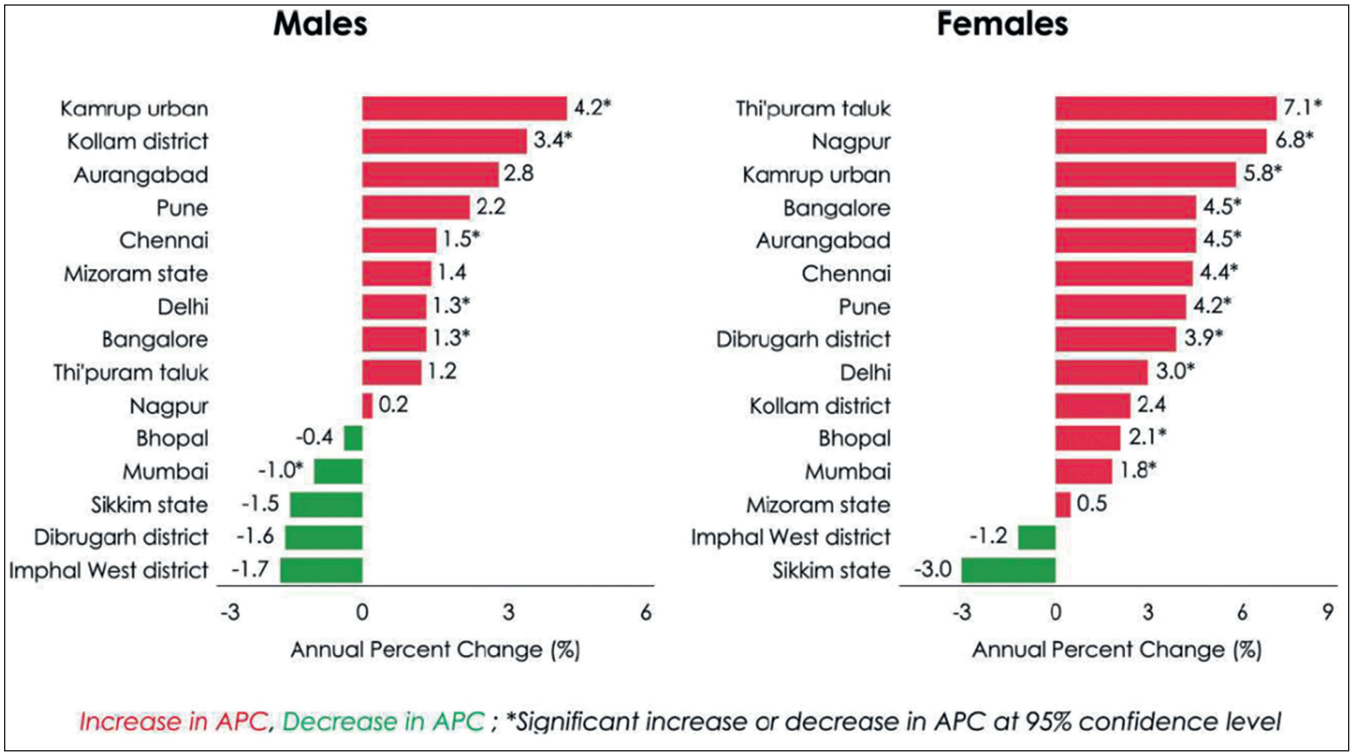

Figure 9. Annual percent change in AARs over the time period.

Reproduced with permission from: NCRP, ICMR (Open Source)

Table 4. Number of cases (N) registered for cancer lung and its relative proportion to all sites of cancer (%), crude (CR), age adjusted (AAR) and truncated (TR) incidence rates per 100,000 population and its rank in 28 PBCRs under National Cancer Registry Programme in males and females.

Registry	N (%)	CR	AAR	TR	RANK
Males					
Delhi	3249 (10.5)	11.8	16.7	27.9	9
Patiala	374 (6.9)	7.0	7.7	15.8	24
Hyderabad	561 (10.9)	9.2	12.4	18.0	14
Kollam	1833 (18.5)	29.4	23.1	34.7	3
Trivandum	1685 (12.5)	21.3	16.8	27.3	8
Bengaluru	1335 (10.1)	9.8	13.0	19.1	12
Chennai	1397 (9.7)	11.8	11.9	18.1	17
Kolkata	2040 (20.0)	22.0	18.3	28.1	5
Ahmedabad Urban	1188 (8.1)	7.3	8.8	13.9	21
Aurangabad	216 (11.2)	6.4	8.8	14.3	22
Osmanabad and Beed	177 (4.9)	1.9	1.9	3.5	31
Barsi (Rural)	25 (3.4)	1.9	1.8	3.6	32
Mumbai	2554 (9.7)	9.5	11.0	14.5	19
Pune	735 (7.6)	5.1	6.7	9.3	26
Wardha	170 (7.1)	5.0	4.6	8.5	30
Bhopal	390 (10.9)	9.1	12.0	20.2	16
Nagpur	368 (6.2)	5.5	6.1	9.8	28
Manipur	698 (18.9)	8.9	12.9	12.5	13
Imphal West District	215 (14.3)	15.5	16.6	21.5	3
Mizoram	618 (14.3)	20.9	32.1	41.1 2	2
Aizawl	287 (13.2)	27.1	38.8	50.3	1
Sikkim	83 (7.1)	4.9	6.5	8.1	27
Tripura	1103 (16.8)	11.3	14.5	23.1	10
West Arunachal	79 (6.5)	3.7	7.0	14.3	25
Papumpare	38 (8.1)	7.6	20.1	38.0	4
Meghalaya	286 (6.1)	5.6	12.4	21.7	15
East Khasi Hills District	153 (5.3)	6.9	14.1	22.4	11
Nagaland	84 (6.0)	4.5	8.4	12.2	23
Pasighat	25 (7.8)	7.1	9.7	19.8	20
Cachar District	400 (8.6)	8.5	11.9	18.4	18
Dibrugarh	135 (5.3)	3.9	5.1	7.6	29
Kamrup Urban	494 (7.9)	15.1	18.1	23.9	

Registry	N (%)	CR	AAR	TR	RANK
Females					
Delhi	962 (3.3)	4.0	5.1	9.2	13
Patiala	134 (2.2)	2.8	2.8	5.4	26
Hyderabad	262 (4.1)	4.5	6.0	11.6	8
Kollam	359 (3.7)	5.1	3.8	6.8	22
Trivandum	545 (3.8)	6.3	4.7	8.1	15
Bengaluru	596 (3.8)	4.7	5.8	10.5	11
Chennai	555 (3.3)	4.7	4.4	7.7	16
Kolkata	602 (6.6)	7.0	5.9	10.6	9
Ahmedabad Urban	311 (2.8)	2.1	2.4	3.9	28
Aurangabad	79 (3.9)	2.5	3.2	5.7	25
Osmanabad and Beed	93 (2.1)	1.1	1.0	2.1	32
Barsi (Rural)	26 (3.2)	2.1	1.9	3.8	31
Mumbai	1390 (5.1)	6.0	5.9	8.0	10
Pune	449 (4.2)	3.5	4.0	7.0	20
Wardha	85 (3.4)	2.6	2.3	4.6	29
Bhopal	114 (3.2)	2.9	3.6	7.4	23
Nagpur	177 (2.9)	2.7	2.7	5.1	27
Manipur	649 (14.4)	8.3	11.8	14.1	5
Imphal West District	215 (14.3)	15.5	16.6	21.5	3
Mizoram	528 (14.1)	18.0	27.6	30.7	2
Aizawl	304 (16.0)	27.9	37.9	34.1	1
Sikkim	73 (6.5)	4.9	7.1	9.1	6
Tripura	263 (5.4)	2.8	3.3	5.6	24
West Arunachal	46 (3.9)	2.2	5.0	9.7	14
Papumpare	21 (4.0)	4.2	12.8	21.8	4
Meghalaya	116 (4.1)	2.3	4.3	7.9	17
East Khasi Hills District	70 (4.0)	3.1	5.3	8.7	12
Nagaland	37 (3.7)	2.1	4.3	8.2	18
Pasighat	9 (3.0)	2.6	4.2	7.2	19
Cachar District	125 (3.2)	2.8	3.9	6.9	21
Dibrugarh	52 (2.3)	1.5	2.0	3.6	30
Kamrup Urban	181 (3.8)	5.7	6.7	13.1	7

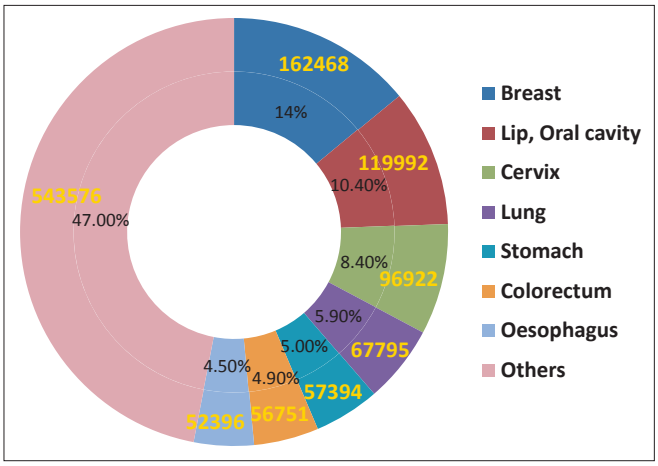

Figure 10. Distribution of new cases of cancer in 2018.

Source: GLOBOCAN, INDIA, 2018[9]

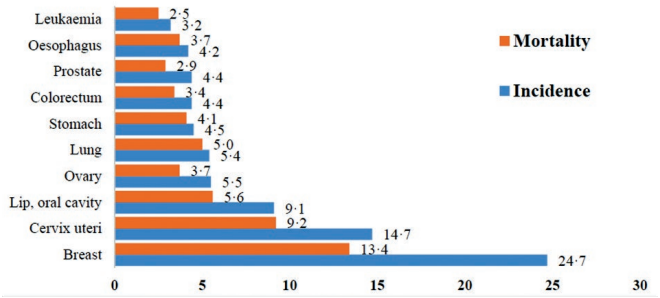

Figure 11. Distribution of estimated age-standardised (World) incidence and mortality rates of 10 major cancers.

Source: WWW.jetir.org

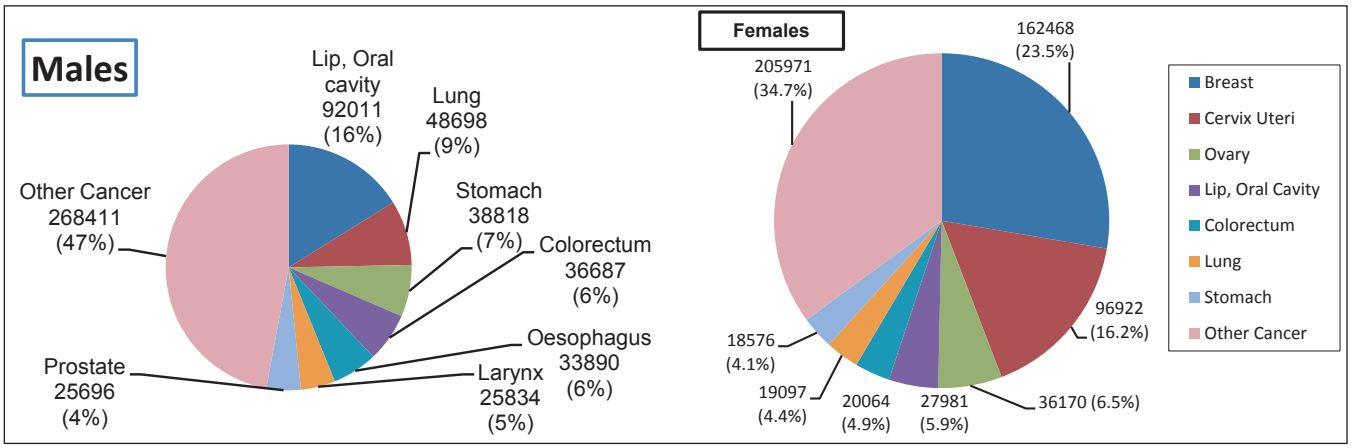

Figure 12. Incidence of major cancers in India in both the sexes for 2018.

Source: GLOBOCAN 2018[9]

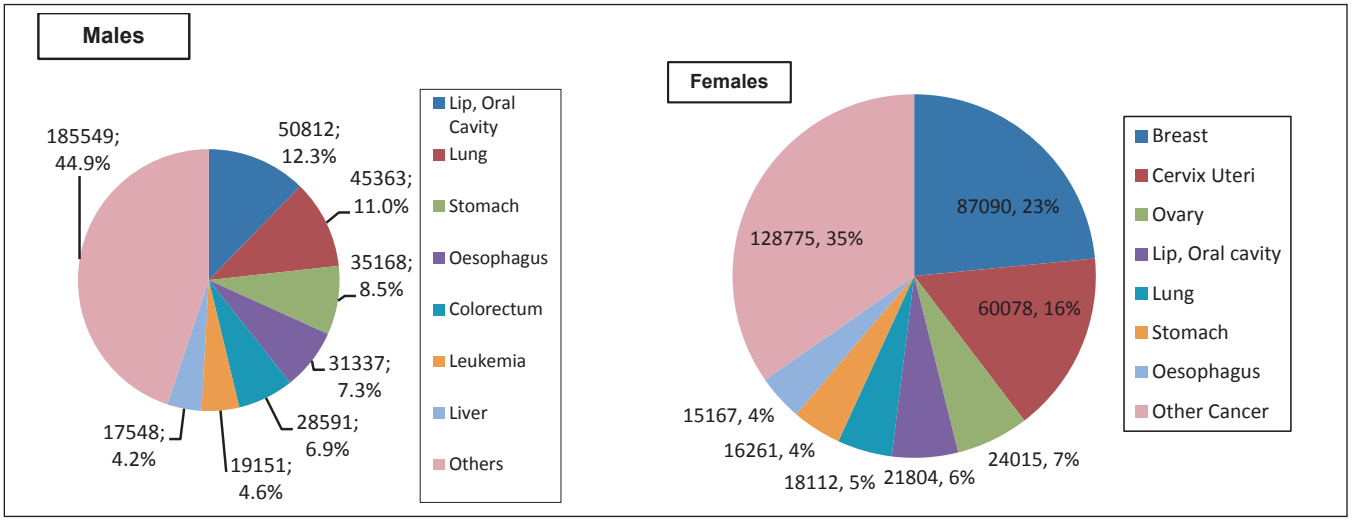

Figure 13. Mortality due to major cancers in India in both sexes for 2018.

Source: GLOBOCAN 2018[9]

Table 5. Summary of cancer statistics in India for the years 2018 and 2020

	Males		Females		Both Sexes	
	2018	2020	2018	2020	2018	2020
Population	701 546 980	717 100 976	652 504 878	662 903 415	1 354 051 855	1 380 004 378
Number of new cancer cases	570 045	646 030	587 249	678 383	1 157 294	1 324 413
Age-standardised incidence rate (World)	89.8	95.7	90.0	99.3	89.4	97.1
Risk of developing cancer before the age of 75 years	9.8%	10.4%	9.4%	10.5%	9.6%	10.4%
Number of cancer deaths	413 519	438 297	371 302	413 381	784 821	851 678
Age-standardised mortality rate (World)	65.8	65.4	57.5	61.0	61.4	63.1
Risk of dying from cancer before the age of 75 years	7.3%	7.4%	6·3%	6.7%	6.8%	7.1%
5-year prevalent cases	1 000 485	1 208 835	1 257 723	1 511 416	2 258 208	2 720 251
Top 5 most frequent cancers (including non-melanoma skin cancer)	Lip, Oral cavity Lung Stomach Colorectum Oesophagus	Lip, oral cavity Lung Stomach Colorectum Oesophagus	Breast Cervix uteri Ovary Lip, Oral cavity Colorectum	Breast Cervix uteri Ovary Lip, oral cavity Colorectum	Breast Lip, Oral cavity Cervix uteri Lung Stomach	Breast Lip, oral cavity Cervix uteri Lung Colorectum
Top 5 cancers in terms of mortality (including non-melanoma skin cancer)	Lip, Oral cavity Lung Stomach Oesophagus Colorectum		Breast Cervix uteri Ovary Lip, Oral cavity Lung		Breast Lip, Oral cavity Lung Cervix uteri Stomach	

Source: GLOBOCAN 2018 and 2020[9,12]

Table 6. Distribution of new cancer cases and deaths in 2018 in India (Data for first 10 common cancers are presented).

Cancer Site	New Cases		Deaths	
	Number (%)	Rank	Number (%)	Rank
Breast	162468 (14)	1	87090 (11.1)	1
Lip, Oral cavity	119992 (10.4)	2	72616 (9.3)	2
Cervix uteri	96922 (8.4)	3	60078 (7.7)	4
Lung	67795 (5.9)	4	63475 (8.1)	3
Stomach	57394 (5)	5	51429 (6.6)	5
Oesophagus	52396 (4.5)	6	46504 (5.9)	6
Leukaemia	42055 (3.6)	7	32471 (4.1)	7
Ovary	36170 (3.1)	8	24015 (3.1)	9
Larynx	28721 (2.5)	9	17640 (2.2)	15
Brain, CNS	28142 (2.4)	10	24003 (3.1)	10

CNS=Central nervous system

data from multiple sources, including 42 PBCRs and the nationwide Sample Registration System of India, to estimate the incidence of 28 types of cancer in every state of India from 1990 to 2016 and the deaths and DALYs caused by them, as part of GBD 2016.

The findings suggested that 8.3% (95% uncertainty interval [UI] 7.9–8.6) of the total deaths and 5.0% (4.6–5.5) of the total DALYs in India in 2016 were due to cancer, which was double the contribution of cancer in 1990. However, the age-standardised incidence rate of cancer did not change substantially during this period. The age-standardised cancer DALY rate had a 2.6 times variation across the states of India in 2016. Ten cancers responsible for the highest proportion of cancer DALYs in India in 2016 were stomach (9.0% of the total cancer DALYs), breast (8.2%), lung (7.5%), lip and oral cavity (7.2%), pharynx other than nasopharynx (6.8%), colon and rectum (5.8%), leukaemia (5.2%), cervical (5.2%), oesophageal (4.3%), and brain and nervous system (3.5%) cancer. There was substantial inter-state heterogeneity in the age-standardised incidence rate of the different types of cancers in 2016, with a 3.3 times to 11.6 times variation for the four most frequent cancers (lip and oral, breast, lung, and stomach). Tobacco use was the leading risk factor for cancers in India to which the highest proportion (10.9%) of cancer DALYs could be attributed in 2016.

The investigators included tracheal, bronchus, and lung cancer as lung cancer for sake of simplicity. The number of incident lung cancer cases in India in 2016 was 67,000 (95% UI 63,000–72,000), 72.2% of which were in males, and the prevalent cases were 74,000 (70,000–80,000). This cancer was the second most common incident cancer among males in 2016. The age-standardised incidence rate of lung cancer varied 8 times in both sexes combined across the states of India in 2016. The crude lung cancer incidence rate in males was highest in Kerala and Mizoram, and in females was highest in Mizoram and Manipur. There was a 6.3 times difference between the highest and lowest state-specific crude DALY rates for lung cancer in 2016. The crude DALY rate for lung cancer in 2016 was highest in Mizoram, followed by Kerala, Manipur, and Jammu and Kashmir. Lung cancer was the first or second leading cause of cancer deaths in 19 states for males (1st in Bihar, Uttarakhand, Tripura, Manipur, Delhi, West Bengal, Msharastra, Kearala, Tamilnadu, Punjab; second in Odisha, Mizoram, Gujrat, Haryana, Telengana, Andhra, J&K, UTS (Union Teritorries) other than Delhi and Himachal Pradesh); and four states for females in 2016 (1st in Mizoran and Manipur; 2nd in Sikkim, J&K). Tobacco use and air pollution were the leading risk factors in GBD for lung cancer in India in 2016 to which 43.2% and 43.0% of the lung cancer DALYs could be attributed, respectively.

As will be seen from figure 14, lung cancer contributed about 7.5% (3rd commonest) of total cancer DALYs in 2016 for both sexes. This was 4.4% in females (7th common) and contributed 10.4% of the total cancer DALYs in males (commonest, first in rank).

Both sexes combined		Females		Males	
Types of cancers*	% of total cancer DALYs	Types of cancers*	% of total cancer DALYs	Types of cancers*	% of total cancer DALYs
1 Stomach cancer	9.0%	1 Breast cancer	16.8%	1 Lung cancer	10.4%
2 Breast cancer	8.2%	2 Cervical cancer	10.5%	2 Lip and oral cavity cancer	9.6%
3 Lung cancer	7.5%	3 Stomach cancer	9.0%	3 Pharynx cancer other than nasopharynx	9.1%
4 Lip and oral cavity cancer	7.2%	4 Colon and rectum cancer	6.1%	4 Stomach cancer	9.0%
5 Pharynx cancer other than nasopharynx	6.8%	5 Lip and oral cavity cancer	4.6%	5 Leukaemia	6.0%
6 Colon and rectum cancer	5.8%	6 Ovarian cancer	4.6%	6 Colon and rectum cancer	5.6%
7 Leukaemia	5.2%	7 Lung cancer	4.4%	7 Oesophageal cancer	5.1%
8 Cervical cancer	5.2%	8 Leukaemia	4.3%	8 Larynx cancer	4.8%
9 Oesophageal cancer	4.3%	9 Gallbladder and biliary tract cancer	4.3%	9 Liver cancer	4.6%
10 Brain and nervous system cancer	3.5%	10 Pharynx cancer other than nasopharynx	4.3%	10 Brain and nervous system cancer	4.0%
11 Liver cancer	3.5%	11 Oesophageal cancer	3.5%	11 Non-Hodgkin lymphoma	3.7%
12 Non-Hodgkin lymphoma	3.2%	12 Brain and nervous system cancer	2.9%	12 Prostate cancer	2.9%
13 Gallbladder and biliary tract cancer	3.1%	13 Non-Hodgkin lymphoma	2.6%	13 Pancreatic cancer	2.6%
14 Larynx cancer	3.0%	14 Liver cancer	2.3%	14 Gallbladder and biliary tract cancer	2.1%
15 Pancreatic cancer	2.4%	15 Pancreatic cancer	2.2%	15 Bladder cancer	1.5%
16 Ovarian cancer	2.2%	16 Uterine cancer	1.7%	16 Nasopharynx cancer	1.4%
17 Prostate cancer	1.5%	17 Thyroid cancer	1.3%	17 Hodgkin's lymphoma	1.2%
18 Bladder cancer	1.1%	18 Larynx cancer	1.1%	18 Multiple myeloma	1.0%
19 Nasopharynx cancer	1.0%	19 Multiple myeloma	1.0%	19 Kidney cancer	0.9%
20 Thyroid cancer	1.0%	20 Nasopharynx cancer	0.7%	20 Thyroid cancer	0.7%
21 Multiple myeloma	1.0%	21 Hodgkin's lymphoma	0.6%	21 Testicular cancer	0.5%
22 Hodgkin's lymphoma	0.9%	22 Bladder cancer	0.6%	22 Mesothelioma	0.4%
23 Uterine cancer	0.8%	23 Kidney cancer	0.4%	23 Breast cancer	0.3%
24 Kidney cancer	0.7%	24 Malignant skin melanoma	0.2%	24 Non-melanoma skin cancer	0.3%
25 Mesothelioma	0.3%	25 Mesothelioma	0.2%	25 Malignant skin melanoma	0.3%
26 Malignant skin melanoma	0.3%	26 Non-melanoma skin cancer	0.1%		
27 Testicular cancer	0.2%				
28 Non-melanoma skin cancer	0.2%				

Figure 14. Percentage of total cancer DALYs due to different types of cancers by sex in India in 2016.[34]

Compared to 1990, DALYs due to lung cancer changed from 7th position to 3rd position in 2016. This was a 136.0% (106.5 to 157.8) mean percentage change in number of DALYs, a 54.9% (35.6 to 69.2) mean percentage change in crude DALY rate, and 15.3% (1.1 to 26.2) mean percentage change in age–standardised DALY rate, between 1990–2016 (95% UI), indicating its significance for India.

Some variation in the number of cancers diagnosed in India in 2012, according to GLOBOCAN estimates, was 1,157,294, *versus* 1,069,000 in the GDB India study. The GBD study, which reported on 28 types of cancers, used data from 42 PBCRs in India, whereas GLOBOCAN 2018, which reported on 36 types of cancers, was based on *Cancer incidence in five continents* (*volume XI*)[35] and used data from 16 Indian cancer registries. Both studies used the data available in their selected population-based cancer registries from 2008 to 2012 to calculate estimates of cancer incidence between 2016 and 2018. Unfortunately, the data from different PBCRs vary in accuracy, which might be the reason why GLOBOCAN 2018 only retrieved data from the 16 cancer registries, they deemed were of better quality to estimate the incidence. Similarly, according to the GBD study, the highest estimate of crude cancer incidence in India was in the state of Kerala[35] (135.3 per 100,000 people), which may not be a true reflection. The data from Kerala were retrieved from the population-based cancer registry maintained by the Regional Cancer Centre in Trivandrum.[35] This registry has better manpower, infrastructure, and resources to capture accurate cancer data from the region than registries in the rest of India. The average life expectancy in Kerala is seven years higher than that of the rest of India (mean 67.9 years *versus* 74.9 years), which might be due to a better socio-demographic index and health-care delivery system in the region.[35] Both the data published indicated that lung cancer in India is growing and is a matter of concern.

The GLOBOCAN-2020 data released in December 2020 for India[12] showed that lung cancer continues to be a growing problem for the country (Figures 15, 16). Five most frequent cancers in 2020 according to GLOBOCAN are given in table 5. The age-standardised incidence and death rates in India are shown in figure 16.

The other source of clinical information on lung cancer in India is through clinical studies and publications from different authors throughout the country (Tables 7 and 8). These publications as depicted show the pattern of the disease including the age and sex profile and the cell type of lung cancer with the relationship of smoking (Tables 7 and 8).[36-105]

Various other authors have highlighted some other important issues on lung cancer in India.[106-111] About eight years back a mini-symposium on lung cancer epidemiology provided a contemporary view of lung cancer epidemiology from tertiary care centers in West, South, and East India.[26,69,70,112] In this context, we had shared our assessment of the clinico-epidemiological profile of lung cancer in North India at that time.[113] One of the most important observations by us in North India (our center) was the lack of change in the distribution of different histologic types with time. At our center, squamous cell carcinoma continued to remain the most common histologic type overall as well as amongst smokers (approximately 38%).[114] Frequency of other

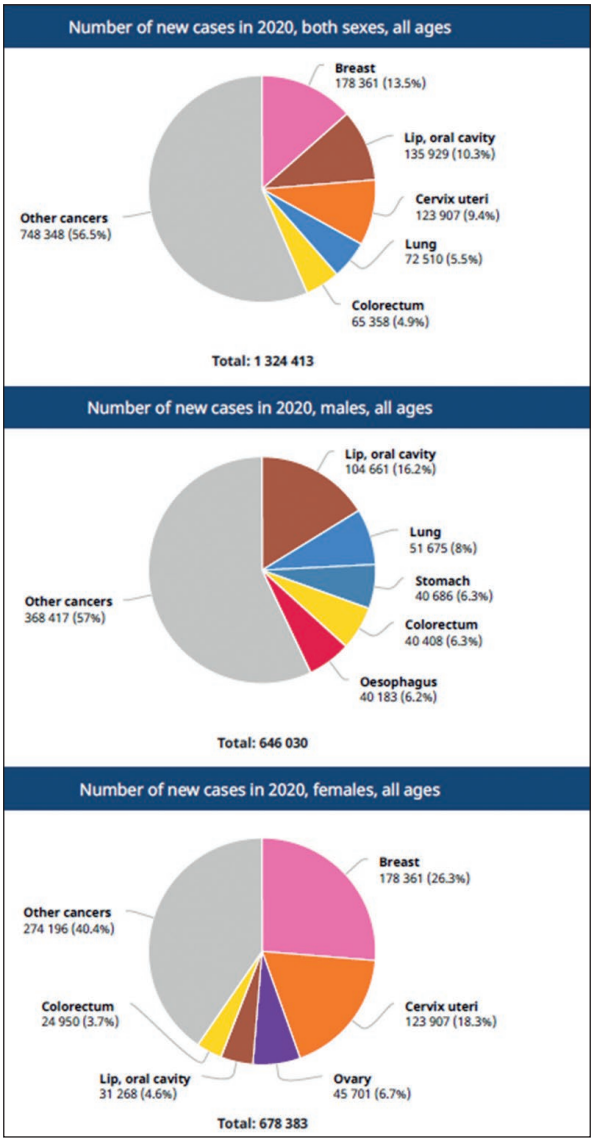

Figure 15. Distribution of new cases of lung cancer in India, sex-wise in the year 2020.

Source: GLOBOCAN 2020[12]

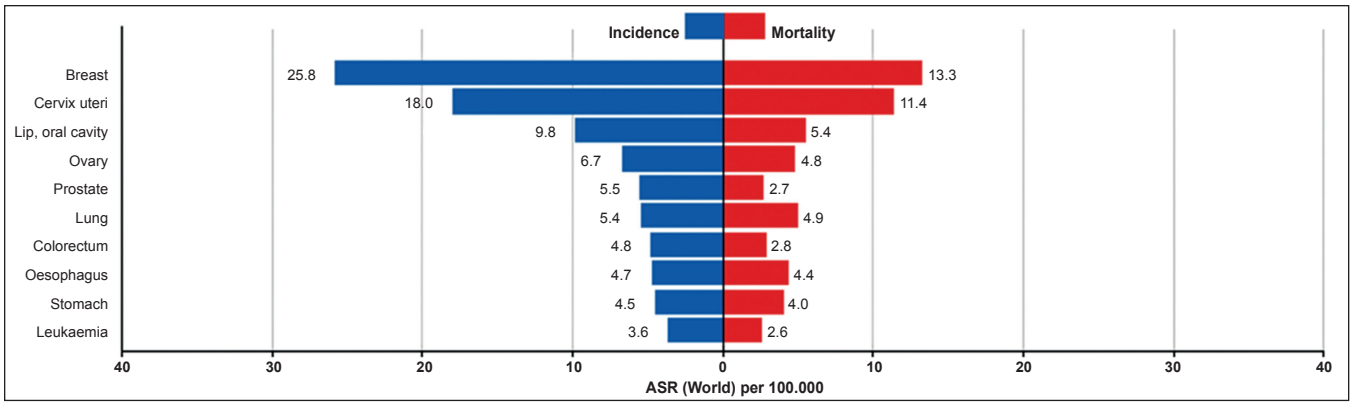

Figure 16. Age-standardised (World) incidence and mortality rates for top 10 cancers in India for 2020.
Source: GLOBOCAN-2020[12]

Table 7. Lung cancer as reported from different Indian studies (1962-2001)

Authors[Ref] and Year	Total	M:F	Age (Years)	S:NS	Squam (%)	Ana (%)	Adeno (%)	UC (%)
Viswanathan *et al*[36] 1962	95	–	–	–	50.5	–	28.4	21.1
Wig *et al*[37] 1961	65	4.9	55.8	–	–	–	–	–
Basu and Ghosh[38] 1971	24	7	48.3	5	62.5	8.3	25	4.2
Sinha[39] 1961	33	4.5	57.1	–	–	–	–	–
Karai *et al*[40] 1967	100	24	52.1	–	41	–	20	39
Shankar[41] 1967	20	All M	54	5.7	73.3	6.7	20	–
Nagrath *et al*[42] 1970	35	4	47.7	1.9	25.7	–	34.3	40
Reddy *et al*[43] 1970	46	6.4	50	0.1	50	25	25	–
Guleria *et al*[44] 1971	120	7.6	57.2	2	46.2	36.5	17.3	–
Jha *et al*[45] 1972	25	2.9	46.6	5.3	44	20	20	20
Nafae *et al*[46] 1973	25	All M	51	7.3	56	20	12	12
Malik and Aikal[47] 1976	136	5.2	48.5	3.5	40.4	21.3	16.9	7.3
Narang *et al*[48] 1977	58	8.7	51.3	4.8	37.9	51.8	10.4	–
Jindal *et al*[49] 1979	150	5.5	51.7	2.4	32.5	19.3	15.8	21.9
Notani and Sanghavi[50] 1974	520	–	–	3.9	27.5	11.3	7.3	53.4
Garg *et al*[51] 1973	82	–	–	–	46.3	28	20.7	–
Malhotra *et al*[52] 1986	70	7.8	49.6	4.8	50	17	14.3	17.1
Jindal and Behera[53] 1990	1009	4.5	54.3	2.7	34.3	27.6	25.9	12.2
Arora *et al*[54] 1990	100	4.05	40-60	1.2	27	1	21	41
Rao *et al*[55] 1992	539*	–	–	–	–	–	–	–
Rajasekaran *et al*[56] 1993	232	7.9	53	2.7	72	4.3	3.9	15.1
Gupta *et al*[57] 1998	279	7.41	56.7	4.5	42.3	32.2	19.9	5.6
Thippanna *et al*[58] 1998	160	8.4	40-60	4	67.5	8.8	18.7	5.1
Arora *et al*[59] 1998	200*	–	–	–	–	–	–	–
Gupta *et al*[60] 2001	265	7.8	50-70	3.6	60	21.5	16.2	2.3
Kashyap *et al*[61] 2001	638**	6.17	54.6	2.4	58.3	–	10.81	–

*=Data described only for those below 40 years of age; **=Data reported for 281 cases of *bidi* smokers, *quoted in Ref No. 46.*

Table 8. Lung cancer as reported from different Indian studies (2004–2020).

Author[Ref] and Year	Place	N	Age	M:F	S:NS	Squam %	Ade %	Large %	Small %	NOS %
Prasad *et al*[62] 2004	Lucknow	400	57	4.3:1	7:3	46.5	18.5		18.2	
Khan *et al*[63] 2006	Kashmir	321		92:8	88:12	77.1	–	–	17.3	–
Rawat *et al*[64] 2009	Dehradun	203	40-60	8.2:1	4.5:1	44.83	19.7	8.37	16.75	10.34
Prasad *et al*[65] 2009	Lucknow	799	58	6:1	3.5:1	47.3	18.3	10.5	13.8	10.1
Kaul *et al*[66] 2010	Kashmir	462	40-69	6.2:1	82:18	67.5	3	<1	20.8	1-2
Sheikh *et al*[67] 2010	Kashmir	783	57.8	685:98	2.4:1	71.3	4.4		20.8	3.6
Bhattacharya *et al*[68] 2011	Kolkata	266	41-60	6.6:1	4:1	35.34	15.79	1.88	13.9	33.08
Dey *et al*[69] 2012	Kolkata	607	60.37	4.14:1	74:26	35.1	30.8	5.9	16.5	11.7
Noronha *et al*[70] 2012	Mumbai	489	56	3.5:1	58:42	26.8	43.8	2.1	8	8.3
Bhaskarapillai *et al*[71] 2012	Malabar, Keral	281	> 50	6.03:1	4:1	13.9	10.7	NSCC 17	5.7	47
Mandal *et al*[72] 2013	Manipur	466	>60	1.1	78.8	49.1	30.8	3	14.8	1.5
Malik *et al*[73] 2013	New Delhi	434	55	4.6	68	29.4	48	1.89	14.7	20.54
Sundaram and Sanya[74] 2014	Kolkata	60	63	4.3	71.4	43.3	31.7	3.2	10	
Yogeesha *et al*[75] 2014	Mangalore	61	60-69	6:1	3:1	–	–	–	–	–
Dubey *et al*[76] 2015	Ujjain	47	41-60	4.2:1	4:1	40.9	34	2.2	6.3	22.7
Pandhi *et al*[77] 2015	Amritsar	150	59.3	60	41	36		3	13	7
Baburao and Narayanswamy[78] 2015	Bangalore	96	61-80	3.1	69.7	47.9	28.1	3.1	12	8.3
Dhandapani *et al*[79] 2016	Chennai	54	59.8	4:1	59.3:40.7	35.2	42.6	–	5.6	16.7
Pujari *et al*[80] 2016	Pune	82	61	4:1	63.4% S	24.4	57.3	1.2	6.09	9.79
Bhadke *et al*[81] 2016	Yavatmal, Maharastra	94	60-70	2:1	54:40	32	48	2	8	10
Kumar *et al*[82] 2016	Udaipur	110	58.1	5.6 :1	82	36	40.9	2.7	20	1.8
Kshetrimayum *et al*[83] 2016	Lucknow	116	55.5	3:1	1.6:1	26.7	60.3	–	7.8	5.2
Neliyathodi *et al*[84] 2016	Mallapuram	41	62.66	4:1	–	65.8	34.1	–	–	–

Author[Ref] and Year	Place	N	Age	M:F	S:NS	Squam %	Ade %	Large %	Small %	NOS %
Mohan *et al*[85] 2016	New Delhi	397	57.8	7.4:1	3.6:1	30	28.6	1.7	14.6	
Kaur *et al*[86] 2017	Chandigarh	1301	58.6	4:1	77%	36.4	36.4	2.8	19.2	5.1
Nair *et al*[87] 2017	Trivandrum	1178	60-64	Males common	Smoker common	12.9	28.5		4.9	12.8
Singh and Rohtagi[88] 2017	Max Hospital, Delhi	421	62	78:21	–	23.3	53	2.8	7.6	11.2
Sreekala *et al*[89] 2017	Trivandrum	160	50-59	6.6:1	8:1	28.8	41.9	2.5	16.6	10.6
Sharma *et al*[90] 2017	Wardha	62	61.4	3:2	1:1	19.35	51.6	4.8	24.2	–
Vasu *et al*[91] 2017	Central Kerala	100	62.5	19:1	–	17	40	–	12	31
Lakshmaiah *et al*[92] 2017	Bengaluru	304*	41-60	3:1	1.78:1	54.3	46.7	–	–	–
George *et al*[93] 2017	Kottayam	81	65.25	8:1	6.4:1	17.3	41.9	7.4	17.3	16
Soman *et al*[94] 2018	Pondichery	116	60.04	2.68 :1	56.34	18	68.16	–	10.6	–
Agrawal *et al*[95] 2018	Bareili	393	63.3	4.7 :1	3.2:1	21.9	29.3	12	12.7	24
Sarfraj *et al*[96] 2018	Jammu	80	59.9	5:15:1	7.8:1	72.72	3.75	–	21.81	–
Dattatreya *et al*[97] 2018	Hyderabad	446	60	2:1	7:3	11.6	66	0.5	2.9	19
Thakkar *et al*[98] 2019	Ahmedabad	50	59.9	9:1	46:4	32	36		4	28
Pandey *et al*[99] 2019	Bihar	157	55	1.5	–	–	–	–	–	–
Ahmed *et al*[100] 2019	Srinagar	142	61-70	3:1	0.75:1	43.6	31	3	22	–
Raghvendra *et al*[101] 2019	Vizianagaram	104	57.8	2.3:1	2.1:1	17.3	76	–	4.8	6
Premananth *et al*[102] 2019	Madurai	50	50-59	2.57:1	3:1	36	50	–	2	
Gaur *et al*[103] 2020	Lucknow	201	46-60	3:1	3:2	35.82	56.72	–	3.98	1.5
Darling *et al*[104] 2020	Army Hospital, New Delhi	136	57.6	2.48:1	2:1	35.3	44.8		NET$154	4.4
Mohan *et al*[105] 2020	New Delhi	1862	59	83:17	76:24	28.6	34	–	16.1	21.4

M=Male, F=Female, N=No. of patients, S=Significant, NS=Not significant, Squam=Squamous, Ade=Adeno

histologic types has also remained similar to what was witnessed at our center three decades ago.[53] In addition to histology, the other clinico-epidemiological variables, namely gender, disease stage, and smoking profile have also not changed substantially with time.[114] However, the authors observed a change since then; and majority of 1301 patients who had advanced disease (Stage IIIB = 30.1%; IV = 53.3%) were males (82.3%) and current/ex-smokers (76.9%).[86] Adenocarcinoma and squamous cell carcinoma (36.4% each) were equally prevalent. As compared to our previous study (1,131,140), adenocarcinoma increased (36.4% *versus* 27.5%) and NSCLC-not otherwise specified (NSCLC-NOS) decreased (5.1% *versus* 10.9%) significantly (P<0.001). The present study had more heavy smokers (68.3% *versus* 61.1%; P=0.013) and median smoking index (SI) was also higher (500 *versus* 400; P=0.001). Among SI-based groups, significant differences were observed for age, gender, body mass index, histology, TNM stage, and metastatic disease distribution. Reduction in NSCLC-NOS had led to adenocarcinoma and squamous cell carcinoma being equally prevalent at their centre in North India, despite an increase in heavy smokers. Accurate histological NSCLC sub-typing is necessary for optimal epidemiological assessment.[86] The second important observation at that time[113] was the presence of significant differences in the key clinico-epidemiological characteristics between current/former smokers and non-smokers. Current/former smokers had higher mean age, higher percentage of males, higher frequency of squamous and small cell histologies as well as lower percentage of advanced NSCLC.[113] Furthermore, when we assessed for presence of these differences in relation to quantified smoking status (using the SI)[115] amongst NSCLC patients, the authors observed a strong and the inverse association between heavy smoking and presence of advanced stage as well as of extra-thoracic disease (ETD) at diagnosis.[116] On multivariate analysis, heavy smoking had significantly lower odds as compared to never-smokers for the presence of advanced NSCLC (odds ratio [OR] = 0.25; 95% confidence interval [CI] = 0.11-0.61) and for ETD (OR=0.29; 95% CI=0.16-0.53). Even on subgroup analyses by histology and gender, the inverse and independent association of heavy smoking with advanced disease and ETD was consistently observed amongst NSCLC patients. Interestingly, non-squamous histology had significantly higher odds as compared to squamous histology for the presence of ETD (OR=2.31; 95% CI=1.50-3.57). The third important association that they have noted has been the high incidence (approximately 45%) of low body mass index (BMI) among newly diagnosed lung cancer patients.[117] Here again, heavy smoking was found to have an independent association with the presence of low BMI (OR=3.74; 95% CI=1.59-8.80). *Bidi* smoking is the most common type of smoking product in India overall, and the same has been observed by the authors amongst lung cancer patients presenting to our center.[116,118] The issue will be discussed in more detail later. It is possible that some or all of the above-mentioned observations are in part linked to the continued predominance of *bidi* smoking in North India. These data also suggest that India has geographical diversity not just for its population profile, but even for a disease, like lung cancer. Longitudinal studies can help to assess whether temporal trends that have been witnessed globally and perhaps in some geographical regions of India are observed in other areas as well.

Updated data extracted from the NCRP of the ICMR showed that East Khasi Hills district of Meghalaya had the highest relative proportion of cancers associated with the use of tobacco, (70.4% for males and 46.5% for females).[119] The higher proportion of cancers associated with the use of tobacco was in the North-Eastern states, followed by registries in the West and Central regions). Lung (9 PBCRs), mouth (9 PBCRs), oesophagus (5 PBCRs), stomach (4 PBCRs), and nasopharynx (1 PBCR) cancers were the most common cancers in males. Lung cancer was the leading site in metropolitan cities and the southern region, whereas mouth cancer was the leading site in the West and Central regions. Lung cancer and oral/mouth cancer were the most common cancers among males in the Indian subcontinent. The projected incidence of patients with cancer in India among males was 679,421 (94.1 per 100,000) and among females 712,758 (103.6 per 100,000) for the year 2020. One in 68 males (lung cancer), 1 in 29 females (breast cancer), and 1 in 9 Indians will develop cancer during their lifetime (0-74 years of age). The projected five most common cancers in 2020 for males (lung, mouth, prostate, tongue, and stomach) constitute 36% of all cancers and for females (breast, cervix uteri, ovary, corpus uteri, and lung) constitute 53% of all cancers. The number of lung cancer cases in males is projected to be 71788 and for females it will be 26490 with a total of 98278 cases (Table 9). The crude rate and cumulative risk of lung cancer in India for both the sexes for 2020 are shown in table 9. The majority of the patients with lung cancer were diagnosed with distant metastasis in males (44.0%) and females (47.6%); (Figure 17).

North-Eastern region of the country has the highest burden of cancer as reported in the Cancer Registry. The PBCR in Tripura (2010-2014) was published recently.[120] The protocol collected data on all cancer cases from Tripura. A total of 10251 cases of cancer of all types

Table 9. Projected incidence of cancer statistics in India, 2020.

Site	Male			Female			Both sexes		
	Patients	CR	Cum Risk	Patients	CR	Cum Risk	Patients	CR	Cum Risk
Lung and bronchus	71788	9.9	1 in 68	26490	3.9	1 in 201	98278	7.0	1 in 101

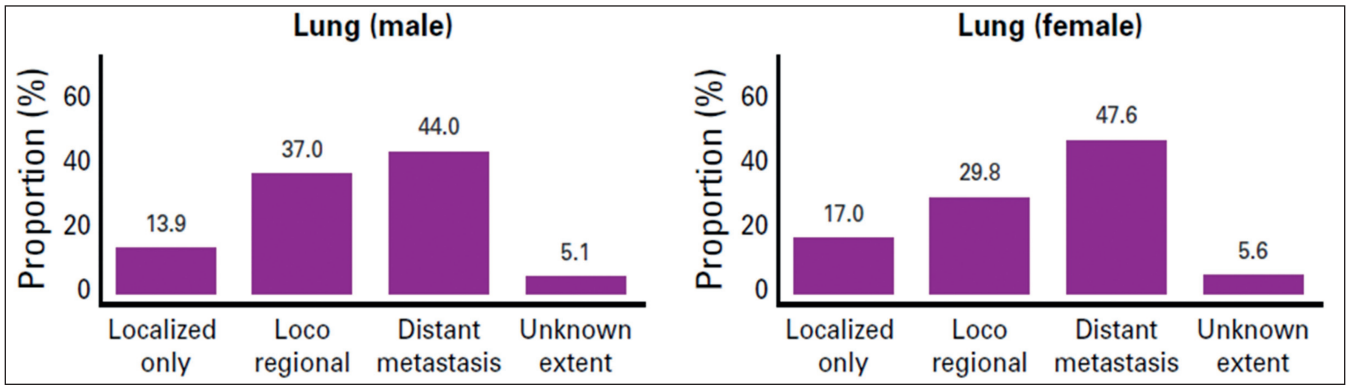

Figure 17. Proportion of cases (%) of lung cancer according to the extent of disease between 2012–2016.

were registered during the period, with an overall age-adjusted incidence rates of 75.7 and 54.9 per 100,000 for males and females, respectively. Crude incidence rate and AAR were among the lowest reported in India, probably due to associated socio-economic factors. The most prevalent cancers were lung (18.1%), and oesophageal (8.3%) for men and cervix uteri (17.6%), breast (13.8%) for females. Rate of cancer mortality in the population was quite high and significantly increased with time, probably accounting for dearth in early detection and feasible treatment alternatives. Tobacco-related cancers were quite high among both men and women with differential distribution of the various sites. While lung and oesophagus cancer were the highest tobacco related cancers in males, oesophageal (5.4%) and lung (4.5%) were the highest among females. For smoking related cancers, among men, highest mortality was due to lung and liver cancers (5-year average mortality to incidence ration [M/I] 61.3, 59.7 respectively). This highlights the fact of regional differences in the country.

The history of cancer with the growing burden in India from antiquity has recently been reviewed.[121] The authors searched PubMed, Internet Archive, the British Library, and several other sources for information on cancer in Indian history. The earliest paleopathology studies from Indus Valley Civilisation sites did not reveal any malignancy. Cancer-like diseases and remedies are mentioned in the ancient *Ayurveda* and *Siddha* manuscripts from India. Cancer was rarely mentioned in the medieval literature from India. Cancer case reports from India began in the 17th Century. Between 1860 and 1910, several audits and cancer case series were published by Indian Medical Service doctors across India. The landmark study by Nath and Grewal[3] used autopsy, pathology, and clinical data between 1917 and 1932 from various medical college hospitals across India to confirm that cancer was a common cause of death in middle-aged and elderly Indians. India's cancer burden was apparently low as a result of the short life expectancy of the natives in those times. In 1946, a National Committee on Health Reforms recommended the creation of sufficient facilities to diagnose and manage the increasing cancer burden in all Indian states. Two publications in 1927 (study over 50 years between 1877-1926) and 1928[122,123] did not mention about lung cancer, even the study refers to similar study of this kind was carried out by Sir Leonard Rogers with regard to Calcutta, and published *under the title as "pathological evidence bearing on disease incidence in Calcutta" by Sir Leonard Rogers, as Glasgow Med J 1925;103(1):1–27).* in January 1925. The 1928 publication has mentioned about 1000 or more cases of various malignant and innocent tumours in Bombay, Calcutta and London, but did not mention about the lung cancer. However, a subsequent study of 4321 autopsy cases between the period 1926-46 at the Grant Medical College, Bombay, the author found 131 tumours and chest tumour was the common form (n=22; 21 in males and 1 in female).[124] Another subsequent study from Calcutta reported 23 cases of lung cancer in males and 11 cases in females in 1954 which constituted 5.7% and 3.2% of the total cancer cases, respectively; and in 1955 there were 49 cases in males and 11 cases in females constituting 9.6% and 2.8% of all cancers, respectively.[125]

Subsequently awareness and interest in lung cancer is growing over the years and rightly so parallel to the rise of the incidence of the disease in India. An

online PubMed search using the words "lung cancer in India" as on 20th October 2020 was made. The nlm.nih.gov website in the PubMed Medline database showed 4900 publications on various aspects of the disease. It is heartening to note that the health-care community in general and oncologists in particular are steadily increasing their contribution to global medical knowledge on lung cancer. From mere one publication in the year 1961, it has crossed 500 in 2019 (Figure 18) and till October 2020, there are 91 contributions already. The real increased after the year 2000 onwards. The citation index of some of the articles from India is really impressive and matches many of landmark publications. This is because some original research work included the largest series of patients of lung cancer from India, showed pharmacogenomic differences in any cancer for the first time in the world and also documented that selection of one of the options from the standard of care can be personalised to optimise outcome based on *hitherto* unknown criteria.[104] Still other publications[20-25] highlight the comparison of features and outcomes among patients of Asian origin (including India) and also document the survival benefit when patients with advanced lung cancer are treated by medical oncologists as opposed to other oncologist or health-care professionals that will be deliberated subsequently.

Histology of Lung Cancer in India

Over the years, there is a gradual but significant change in the histopathology type of lung cancer observed in India. This is shown in Figure 19. It will be noted that adenocarcinoma is now the predominant type of lung cancer in India. This transition is more evident from 2015 onwards, although since 2004, there was a rising trend (squamous cell was still the commonest). This predominant cell type of adenocarcinoma is reported from all major centers of India (Table 8). The NCRP report 2020[32] of the ICMR has also revealed that adenocarcinoma is the predominant cell type in India, both in males and females (Table 10).

Thus, 52.8% of all female lung cancers and 34.4% of all male lung cancers in India were due to adenocarcinoma which was the commonest cell type in both the sexes. Squamous cell carcinoma was present in 23.5% of males and 11.5% females with lung cancer. Figure 19 shows that the incidence of adenocarcinoma has risen by 2.5 times over a period of about 15 years. This rise of adenocarcinoma of the lung occurred decades after that was seen in lung cancer cell types in other developed countries. Such a rising trend was observed in USA way back in 1977.[126] More recently, while analysing the Surveillance, Epidemiology, and End Results (SEER) data of USA to investigate the changes in incidence, treatment, and survival of lung cancer from 1973 to 2015, it was found that since 1985, adenocarcinoma has become the most prevalent histopathological type.[127] Factors, which in part, may account for this increased prevalence are: (1) changes in the criteria for reading histopathology of lung cancer, particularly since 1967; (2) the increased incidence of lung cancer among the female population who have a propensity for adenocarcinoma; and (3) occupational and environmental factors. It may be pertinent to mention that in India immunohistochemistry (IHC) was not universally available, which is now the recommended method for histology (Table 11). As more and more centers are using IHC, more cases adenocarcinoma are being diagnosed and undifferentiated types are diminishing. Further, as mentioned previously, lung cancer showed significant increase in males and females by 7.2% and 9.0%, respectively between 2003 and 2016 in India.[32]

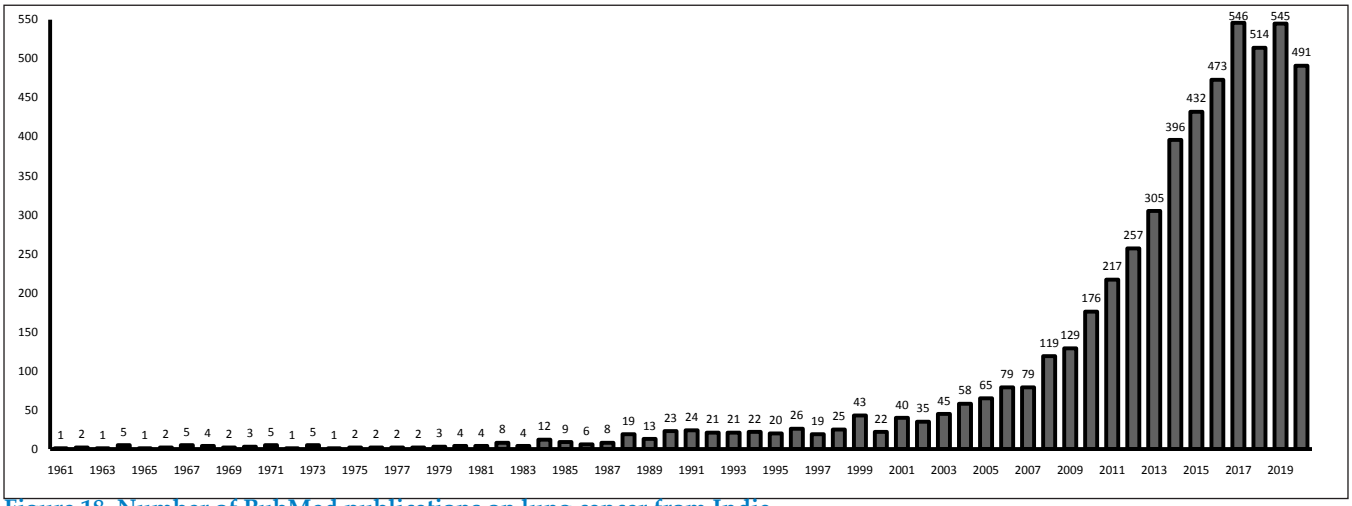

Figure 18. Number of PubMed publications on lung cancer from India.

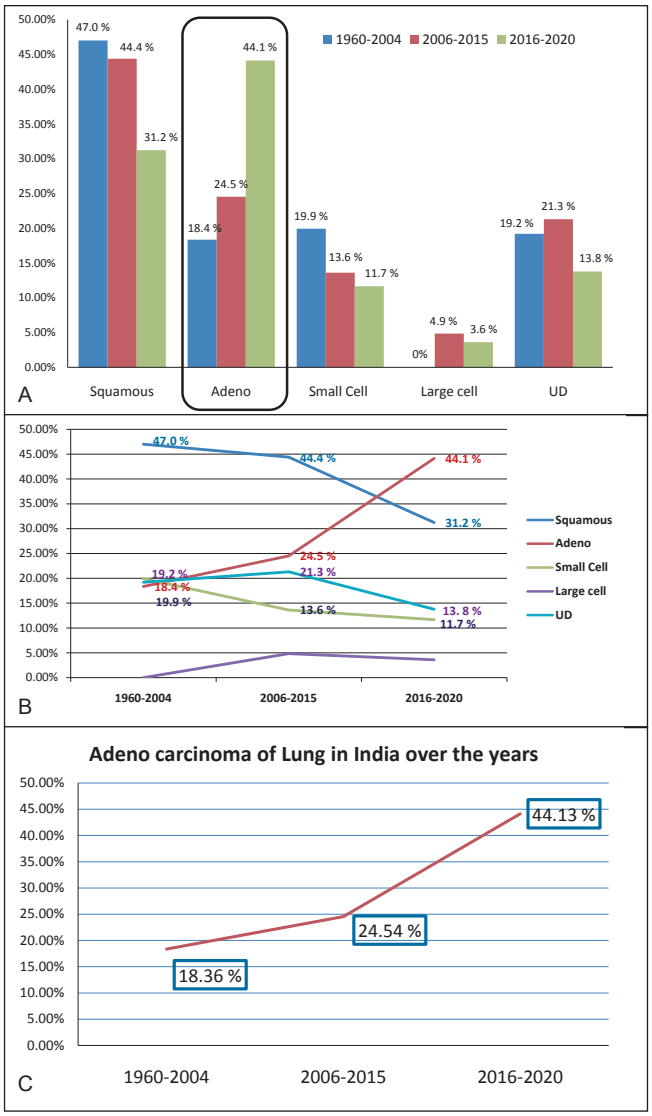

Figure 19 A-B-C. Histological pattern of lung cancer as seen in India over the years.

Table 10. Histological types of lung cancer in India (NCPR data).

Histology	Males	Females
	Number (%)	Number (%)
Epithelial tumours		
Adenocarcinoma	5979 (34.4)	2773 (52.8)
Squamous cell	4083 (23.5)	604 (11.5)
Small cell	1755 (10.1)	317 (6.0)
Non-small cell	2727 (15.7)	619 (11.8)
Others	970 (5.6)	329 (6.3)
Lymph hystiocytic tumours	28 (17)	
Mesenchymal tumours	46 (22)	
Tumours of ectopic origin	2 (10.8)	
Others	1801	573 (11.6)
Total	17391 (100.0)	5254 (100)

Table 11. Recommended immunihistochemistry for lung cancer

Histology	IHC Recommended/Should be Done
Adenoarcinoma	TTF-1, Napsin, CK7
Squamous carcinoma	P40; p63; CK 5/6; desmocolin
Neuroendocrine tumours	Chromogranin, synaptophysin, CD 56

Aetiology of Lung Cancer in Indian Context

The issue was discussed in the earlier review[4]; however, some of the newer information subsequent to that will be presented here.

Smoking

Smoking continues to be the most important factor for lung cancer world-over.[128-131] In patients with lung cancer a history of active tobacco smoking is present in 76% of the cases. One of the important smoking product is *bidi*, which is a major product used by most people in India. Notani and Singhvi[132] way back in 1974 had reported the relative risk of developing lung cancer is 2.6 for *bidi* smokers and 2.2 for cigarette smokers with 2.5 as the overall relative risk in smokers. It was reported also that *Bidi* is more carcinogenic than other products.[133,134] Subsequently, more reports highlighted the risk of *bidi* smoking and lung cancer in India (Table 12).[135-139]

Hookah smoking has also been associated with lung cancer as reported by Nafae *et al.*[46] Subsequently, similar observations were also made from Kashmir,[140] who reported that *hookah* smokers were nearly six times more at risk for lung cancer as compared to non-smokers (OR=5.8, (95% CI=3.9-8.6, P<0.0001). In another study, Gupta *et al*[136] reported that smoking of *bidi* and *hookah* as well as cigarettes had similar ORs for cumulative consumption. The risk increased with both the duration and quantity of all smoking products. Some larger studies on other issues related to smoking and lung cancer in India will be discussed later.

About 25% of lung cancer cases worldwide are not attributable to tobacco smoking. Thus, lung cancer in never smokers is the seventh leading cause of cancer deaths in the world, killing more people every year than pancreatic or prostate cancers. Globally, lung cancer in never smokers demonstrates a marked gender bias, occurring more frequently among women. In particular, there is a high proportion of never smokers in Asian women diagnosed with lung cancer. Although smoking-related carcinogens act on both proximal and distal airways inducing all the major forms of lung cancers, cancers arising in never smokers target the distal airways and favour adenocarcinoma histology.

Environmental tobacco smoke (ETS) is a relatively weak carcinogen and can only account for a small number of lung cancers arising in never smokers. ETS is an important indoor air pollutant that may be a contributing risk factor. A meta-analysis of 41 studies showed that environmental tobacco exposure carries a relative risk of developing lung cancer of 1.48 (1.13-1.92) in males and 1.2 (1.12-1.29) in females.[141] Subsequently, many more reviews have highlighted the issue.[142-144] In a study on non-smoking lung cancer patients, ETS exposure during childhood carries an OR of 3.9 (95% CI 1.9-8.2).[145] There is an increase risk with increase in number of smokers in the house and duration of exposure. Women had high OR of 5.1. Although multiple risk factors, including environmental, hormonal, genetic and viral factors, have been implicated in the pathogenesis of lung cancer in never smokers, no clear-cut dominant factor has emerged that can explain the relatively high incidence of lung cancer in never smokers and the marked geographic differences in gender proportions (Table 13).

Indoor air pollution is an important attributable risk factor for lung cancer in women who are not smokers. In a case-control study, we have shown that in non-smoker females, out of all the cooking fuels, the risk of development of lung cancer was highest for biomass fuel exposure with an OR of 5.33 (95% CI 1.7- 16.7). Use of mixed fuels was associated with a lesser risk (OR= 3.04, 95% CI 1.1-8.4).). In multivariate logistic regression analysis biomass fuel exposure was still significant with OR of 3.59 (95% CI 1.1-12.0) even after adjusting for smoking and passive smoking. This study[146] indicated that biomass fuel exposure is an important risk factor in the causation of lung cancer among women, in addition of exposure to tobacco smoke (Table 14). Similar observations are also made earlier by others.[147-149]

Outdoor air pollution is an important factor in the causation of lung cancer and the subject has been reviewed by many other authors.[150,151] Outdoor air pollution is a major contributor to the burden of the disease worldwide. Most of the global population resides in places where air pollution levels, because of emissions from industry, power generation, transportation, and domestic burning, considerably exceed the WHO's health-based air-quality guidelines. Outdoor air pollution poses an urgent worldwide public health challenge because it is ubiquitous and has numerous serious adverse human health effects, including cancer. Currently, there is substantial evidence from studies of humans and experimental animals as well as mechanistic evidence to support a causal link between outdoor (ambient) air pollution, and especially particulate matter (PM) in outdoor air, with lung cancer incidence and mortality. It is estimated that hundreds of thousands of lung cancer deaths annually worldwide are attributable to PM air pollution. Epidemiological evidence on outdoor air pollution and the risk of other types of cancer, such

Table 12. *Bidi* smoking and lung cancer.

Author[Ref] and Place	Number of Cases Studied	Odds Ratio	
		Bidi	Cigarette
Prasad *et al*[135] Lucknow	284 LC *vs* 852 C	6.1 (14.3- 8.7)	5.3 (2.7- 10.4)
Gupta *et al*[136] Chandigarh	265 LC *vs* 525 C	5.76 (3.4–9.7)	3.86 (2.1-7.0)
Gajalakshmi *et al*[137] Chennai	778 LC *vs* 3430 C	6.45 (4.4–9.5)	4.54 (3.0–7.0)
Notani *et al*[138] Mumbai	683 LC *vs* 1279 C	3.47	2.4 *vs* non-smokers
Jayalekshmy *et al*[139] Kerala	212 cases	3.9 (95% CI = 2.6-6.0) P<0.001)	

Table 13. Passive smoking and lung cancer in Chandigarh.[145]

Timing of Exposure to ETS	OR (95% CI)	Comments
Childhood	3.9 (1.9-5.2)	• Effect for cigarette only • Either smoking father or mother • Risk increases with duration or number
Spouse	5.1 (1.5-17)	Higher OR for women The risk for cigarettes only
Work-place	Weak association	Increases with number of years of exposure
Exposure in vehicles	Risk in non-smokers	

Table 14. Domestic fuel use and lung cancer

Smoking Status	Univariate Analysis		Multivariate Analysis	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Smoking	4.8	1.337-17.753	2.6	0.639-10.70
Passive Smoking	2.9	1.322-6.571	2.1	0.825-4.917
Cooking Fuel				
LPG*	1		1	
Kerosene	2683.4	0.000-Infinity	1827.5	0.000-Infinity
Biomass	5.333	1.700-16.731	3.6	1.079-11.966
Mixed	3.048	1.108-8.381	2.8	0.997-7.950

*Reference

as bladder cancer or breast cancer, is more limited. Outdoor air pollution may also be associated with poor cancer survival, although further research is needed.[152] Indian literature on lung cancer is silent on this specific aspect. Occupational exposure is another important risk factor for lung cancer that was reviewed earlier[4] and more recently.[153,154] Although many Indian reports describe the occupation of lung cancer patients, systematic information on occupation and lung cancer has not been clearly defined from India.

Cancer in women is a matter of great debate. Are they different than men? Current epidemiological data show the increasing female to male incidence ratio for this type of cancer. A high incidence of lung cancer in never smokers with importance of environmental agents makes a problem among women. Adenocarcinoma is noted in women with increasing rate and ethnic background impacts female lung cancer with differences in the incidence of genetic aberrations. The conception of different hormonal status is taken into consideration as potential explanation of variant cancer biology and clinical manifestation in women and men. The impact of 17-β-estradiol, estrogen receptors, aromatase expression, pituitary sex hormones receptors in carcinogenesis with relation between estrogens and genetic aberrations are investigated. Mutation rates particularly the epidermal growth factor receptor epidermal growth factor receptor (EGFR) is more common in never-smokers women. The response to newest therapies among female is also different than in men.[155-157] There are major clinical differences between lung cancers arising in never smokers and smokers and their response to targeted therapies. Indeed, non-smoking status is the strongest clinical predictor of benefit from the EGFR tyrosine kinase inhibitors. The above-mentioned facts strongly suggest that lung cancer arising in never smokers is a disease distinct from the more common tobacco-associated forms of lung cancer. Further efforts are needed to identify the major cause or causes of lung cancers arising in never smokers before successful strategies for prevention, early diagnosis and novel therapies can be implemented. Lung cancer in women in India also is showing a similar trend. In a series of 489 patients from Mumbai, with a median age of 56 years, 255 (52%) were non-smokers and 234 (48%) were smokers and the authors concluded that a considerably higher numbers of Indian patients with lung cancer are non-smokers, compared to the West. The global trend of rise in adenocarcinoma is paralleled in India and they suggested that non-tobacco-related risk factors need further investigation.[26]

Diet, oxidants-anti-oxidant imbalance as possible contributors to development of lung cancer in India was reviewed in our earlier publication.[4]

Genetics and Lung Cancer

A number of genetic factors have been identified in the causation of lung cancer.[158,159] More than 1000 candidate-gene association studies on genetic susceptibility to lung cancer have been published over the last two decades but with few consensuses for the likely culprits. A comprehensive review, meta-analysis and evidence strength evaluation of published candidate-gene association studies in lung cancer up to November 1, 2015 was carried out by Wang *et al*.[160] The epidemiological credibility of cumulative evidence was assessed using standard criteria. A total of 1018 publications with 2910 genetic variants in 754 different genes or chromosomal loci were included. Main meta-analyses were performed on 246 variants in 138 different genes. Twenty-two variants from 21 genes (*APEX1* rs1130409 and rs1760944, *ATM* rs664677, *AXIN2* rs2240308, *CHRNA3* rs6495309, *CHRNA5* rs16969968, *CLPTM1L* rs402710, *CXCR2* rs1126579, *CYP1A1* rs4646903, *CYP2E1* rs6413432, *ERCC1* rs11615, *ERCC2* rs13181, *FGFR4* rs351855, *HYKK* rs931794, *MIR146A* rs2910164, *MIR196A2* rs11614913, *OGG1* rs1052133, *PON1* rs662, *REV3L* rs462779, *SOD2*

rs4880, *TERT* rs2736098, and *TP53* rs1042522) showed significant associations with lung cancer susceptibility with strong cumulative epidemiological evidence. No significant associations with lung cancer risk were found for other 150 variants in 98 genes; however, seven variants demonstrated strong cumulative evidence.[140] Many Indian researchers have also studied various genetic susceptibility issues and genetics associated with lung cancer.[161-196]

Tuberculosis and Lung Cancer

Tuberculosis (TB) is a major health problem in India and is quite prevalent. Lung infections, including TB, have been implicated as potentially contributing to the etiology of lung cancer.[197] TB may increase the risk of lung cancer through substantial and prolonged pulmonary inflammation, leading to host tissue damage, fibrosis, scar formation, and genetic alterations.[197-200] A meta-analysis reported TB to be associated with a 1.7-fold elevation in the risk of lung cancer.[201] However, the majority of prior investigations[197-200] have been case–control studies, and there are very limited prospective data regarding TB and lung cancer risk. As cigarette smoking is such a strong risk factor for lung cancer, it is possible that smoking and TB act synergistically to cause damage to the lungs, and subsequently, increase in lung cancer risk. In another study,[202] 44 lung cancer cases occurred among 273 men with TB (incidence rate of 1786 per 100,000 person-years). TB was associated with a two-fold elevation in lung cancer risk (HR=1.97; 95% CI=1.46–2.65) with significant associations observed for both incident (HR=2.05; 95% CI=1.42–2.96) and prevalent TB (HR=1.82; 95% CI=1.09–3.02). Lung cancer risk was greatest in the 2-year window after TB diagnosis (HR=5.01; 95% CI=2.96–8.48) but remained elevated at longer latencies (HR = 1.53; 95% CI=1.07–2.20). Though TB was associated with an increased risk of squamous cell carcinoma (HR=3.71), adenocarcinoma (HR=1.71), small cell carcinoma (HR=1.72), and lung cancer of other (HR=1.23) and unknown histologies (HR=1.35), only the association for squamous cell carcinoma was statistically significant. TB is associated with an increased lung cancer risk in male smokers.[202] Other studies and reviews had pointed out the association and causation of TB and lung cancer and scar carcinoma.[203-207]

Other Demographic Features of Lung Cancer in India

Detailed demographic features of lung cancer, from other studies as reported by different authors including three major studies with more than 1000 cases are summarised in table 15.

Table 15. Demographic data, presenting symptoms and signs of lung cancer in India

Demographics	Kaur *et al*[86]	Mohan *et al*[105]	Jindal and Behera[53]	Other Indian Studies[4]
Age (years)	Mean+SD 58.6+10.8 Median (IQR) 60 (51-65)	≤45 256 (13.8) 46-70 1410 (75.7) >70 196 (10.5)	Mean age – 54.6 years in males and 52.8 years in females	
Sex				
Male (M) Female (F)	M: 1071 (82.3%) F: 230 (17.7%) M:F::4.6:1	M:1544 (82.9%) F: 318 (17.1%) M:F::4.8:1	Male-to-female ratio ranging from 5.76:1 – 6.67:1 in various studies	
BMI (Kg/m^2)	<16 22.4% >16<18.5 14.5% >18.5 <23 40% >23 23%	–		
Smoking history	Current or Ex-smokers 1000 (76.9%) Non-smokers 301 (23.1%) S:NS:: 3.3:1	Non-smokers 425 (23.8%) Current smokers 697 (39%) Reformed smokers 666 (37.2%) S:NS::3.21:1	Smokers: Non-smokers:: 2.5–2.7:1	

Conti…

Demographics	Kaur *et al*[86]	Mohan *et al*[105]	Jindal and Behera[53]	Other Indian Studies[4]
Smoking index	1-100: 10.7% 101-300: 21.8% >301: 65.5%	<100: 95 (8.4%) 100-300: 254 (22.4%) 301-600: 385 (33.9%) >600: 402 (35.3%)		
Literacy status	-	Illiterate (27.4%) Primary (27.3%) Secondary (matric) 24.4%) Higher secondary (9.9%) Graduation (8.3%) Post-graduation (2.7%)		
Symptoms/Signs (%)				
Cough		81.3	88	40-94.3
Loss of appetite		65.9	90	20.5-70
Dyspnoea		64.9	Not mentioned	24-59
Fatigue (weakness)		60.4	90	4-60
Weight loss		58.1	90	11.4-77
Chest pain		48.9	52.2	16-66.7
Haemoptysis		36.1	69.2	8-60
Fever			19.6	22-68.6
Hoarseness of voice		–	29.9	9-33
Nausea, Vomiting			6	25
Digital clubbing		18.7		
Peripheral-lymph adenopathy		13.3		
Neurological manifestations		2.1		
Superior vena cava obstruction		3.4	19.8	2.9-8.3
Dysphagia			20.8	2.9-6
Others	Not mentioned	Not mentioned	30.5	Not mentioned
Duration of Symptoms		< 3 months in 32.6% – 44% cases, 3-6 months in 16.0%-34.3% cases > 6 months in 21.0% - 24.0 % of cases		
Diagnostic Methods				
Flexible bronchoscopy		890 (50.2)		
CT/USG-guided FNAC/biopsy (lung)		577 (32.6)		
Thoracoentesis		95 (5.4)		
Thoracoscopic pleural biopsy		19 (1.1)		
Peripheral lymph node sampling		100 (5.6)		
EBUS		47 (2.7)		
Lung biopsy (surgical)		6 (0.3)		
Others		38 (2.1)		

In the study by Kaur *et al*[86], majority (76.9%) were smokers, especially heavy smokers (SI = Number of *bidi*/cigarette smoked per day × number of years smoked); SI ≥301; 51.9%). Significant differences were observed in relation to age, gender, BMI, histology, TNM stage, metastatic disease, and extra-thoracic metastasis among SI-based groups. Mean age was highest among heavy smokers. Never smokers were predominantly females (55.5%) and their percentage progressively decreased as SI increased (23.4% in light smokers, 7.8% in moderate smokers, and only 3.1% in heavy smokers). BMI had an inverse relationship with severity of smoking, being the highest in never smokers and lowest in heavy smokers. Overweight/obese individuals (BMI ≥23 Kg/m^2) were most frequent in never smokers (43.2%) and this reduced progressively as SI increased (25.0% in light smokers, 18.9% in moderate smokers, and 15.7% in heavy smokers). Conversely, underweight individuals were highest in heavy smokers (41.2%) and lowest in never smokers (20.7%). In an earlier study[117], it was reported that low BMI is common among newly diagnosed lung cancer patients in North India. Heavy smoking is independently associated with the presence of low BMI at presentation among NSCLC patients.[208] Even for histological distribution, as SI increased, a progressive decrease in the prevalence of adenocarcinoma (66.8% *versus* 37.4% *versus* 33.0% *versus* 23.9%) accompanied by progressive increase in squamous cell carcinoma (9.6% *versus* 32.7% *versus* 40.4% *versus* 47.7%) was observed. Frequency of SCLC was the lowest in never smokers. There was an inverse relationship of smoking status with disease stage at presentation (Stage IV being highest in never smokers [77.1%] and lowest in heavy smokers [43.6%]). Conversely, Stage IIIB increased progressively as SI increased (17.6% *versus* 27.1% *versus* 31.2% *versus* 35.9%). All groups had <5% patients in Stages I–II. Extra-thoracic metastatic disease at presentation was also highest amongst non-smokers and reduced progressively in light, moderate, and heavy smokers. On subgroup analysis based on histology, stage distribution was significantly different with percentages of Stages I–IIIA *versus* IIIB–IV being 24.9% *versus* 75.1% in squamous cell carcinoma, 11.6% *versus* 88.4% in adenocarcinoma, 20.4% *versus* 79.6% in NSCLC-NOS/large cell NSCLC, and 8.8% *versus* 91.2% in SCLC (P<0.0001). Among newly diagnosed NSCLC patients in North India, significant differences exist, based upon SI, for disease stage. Heavy smoking was independently associated with lower odds of having advanced stage as well as with lower odds of having extra-thoracic disease at the time of diagnosis[209], although the authors concluded that this needs confirmation through a larger studies. The demographic profile of the reported cohort (time period 2011–2015) was compared with previous (time period 2008–2011) from the same center at PGI, Chandigarh. Although there was no change in age/gender distribution and ratio of current/ex-smokers to never smokers (3.3:1 in both cohorts), percentage of heavy smokers among all current/ex-smokers increased significantly from 59.8% to 67.5% in between the two study periods. Median (IQR) SI was also higher (500 [290–800] *versus* 400 [240–700]; P=0.001). Histological distribution also changed significantly (adenocarcinoma increased from 27.5% to 36.4% [P<0.001]). However, on analysing squamous cell carcinoma *versus* all other types (non-squamous NSCLC and SCLC), statistical significance was not achieved (P=0.47). Stage distribution could not be compared as different TNM classification schemes were used during the two study periods (6th and 7th edition of the IASLC).

The PGI, Chandigarh has done continuous evaluation of the clinico-epidemiological profile of lung cancer over the years in that centre and it has shown several interesting observations. While the initial publication involving 250 patients few years back showed no change as compared to the profile observed three decades earlier, the next publication with greater number of patients (>650) showed that quantified tobacco smoke exposure (QTSE) is able to categorise patients into groups that differ significantly among each other in terms of age, gender, histology, stage, and BMI distribution. Going further with the current analysis with a large number of lung cancer cases with a cohort size of 1300+ patients, the authors were able to document two important observations: First, the observations related to SI-based groups (never, light, moderate, and heavy smokers) in the previous publication have been replicated in the current study. Thus, QTSE was able to segregate patients with distinct clinico-epidemiological profiles with heavy smokers (SI ≥301) characterised by higher age, predominantly male gender and squamous histology, lower BMI, and lesser prevalence of Stage IV/extra-thoracic metastatic disease at one end and never-smokers characterised by younger age, predominantly female gender and adenocarcinoma histology, higher BMI, and higher prevalence of Stage IV/extra-thoracic metastatic disease at the other end. The strength of this current analysis as compared to previous one is not only a two-fold increase in number of patients but also that SI-based groups continued to show these differences even when the denominator was all histological types and not just NSCLC (latter being the denominator for the previous analysis). This also lends support to small cell lung cancer (SCLC) being equally well staged as NSCLC using 7th TNM staging system, something which are

already carrying out in routine clinical practice by the group. Majority of patients had locally advanced/metastatic disease which is similar to the previously reported observations. Secondly, results of the current analysis and its comparison with their previous study revealed a changing trend in histological distribution of lung cancer at diagnosis. Both previous and current cohorts included consecutive patients registered. Increasing adenocarcinoma prevalence in the current cohort has occurred in conjunction with a reduction in NSCLC-NOS (undifferentiated NSCLC). Numerically, SCLC appeared to be lesser in the current cohort. However, statistical analysis showed no difference even if patients were categorised into three broad groups, viz small cell lung cancer, squamous cell and non-squamous NSCLC.

While one of the earliest reports (almost 25 years ago) from this center comprising >1000 patients had frequencies of squamous cell carcinoma and adenocarcinoma of approximately 34% and 26%, respectively, it refers to an era wherein histological classification was primarily based on microscopy alone with minimal/no use of immunochemistry.[53] Histological distribution observed was almost similar in a subsequent assessment and comparison published by us five years ago. *Bidi* smoking is known to provide a concentration of carcinogens similar to that of an unfiltered cigarette, and that is why one *bidi* is considered to be equivalent to one cigarette for calculating time intensity (smoking pack-years/SI). This hypothesis is to some extent substantiated even in the subsequent studies wherein squamous cell type continues to be >35% in the backdrop of increasing percentage of heavy smokers and similar overall percentage of current/ex-smokers. However, what is clearly different is that unlike previous papers, frequency of NSCLC-NOS (undifferentiated NSCLC) has reduced successively with time (20% in initial studies to 10% in subsequent analysis and in the latest publication down to 5%.[86] The most likely reason for change in histological distribution seems to be an improvement in histological classification. The current WHO classification puts more emphasis on using molecular and immune-histo/cyto-chemical techniques for accurate diagnosis in small biopsy/fine-needle aspiration cytology samples.

The major limitation of this study[86] is that the patient population and consequently analysis was akin to that of a hospital-based cancer registry. Being retrospective in nature and having associated inherent flaws of such a study design, it can not necessarily extrapolate these observations to population-based data. However, even the available population-based cancer registries in India (http://www.icmr.nic.in/ncrp/cancer_reg.htm) do not include QTSE, and hence, it is not feasible to carry out such an analysis from the published data. The other major limitation is that since this a cross-sectional analysis, it was not possible to provide prognostic role of histological subtype and stage similar to what had been done in longitudinal (prospective and retrospective) studies. These results suggest the persistence of smoking as a risk factor for lung cancer in India with a greater percentage of heavy smokers in comparison to previous studies from that center. Implementation of strict tobacco control measures seems to be the only measure that is likely to reverse the ratio of current/ex-smokers to never smokers and also to prevent and reduce lung cancer incidence. The study also reinforces the need for reporting pathologists and cytologists to use immunochemistry to accurately classify lung cancer histological type as per guidelines; frequency of NSCLC-NOS continues to be lowest among major cancer centers in India – a country wherein geographical diversity is manifest even in a disease such as lung cancer.

Another study from AIIMS, New Delhi, which is a 10-year analysis from the largest single centre study to evaluate the clinical spectrum of lung cancer in India, revealed some interesting trends.[105] The average age of patients was 58 years, which is similar to that reported in previous Indian studies, but almost 10 years less than the mean age reported in most Western studies.[53,72,113,114] No changing trend in age was seen during the study period. Similarly, the male predominance was similar to other Indian reports but higher than the Western studies. This may be a reflection of higher smoking prevalence in females in the West or possibly due to the fact that males tend to seek medical attention more frequently than females in our societal set-up. However, the authors observed a definite increase in the proportion of females from 7.9% in 2008 to 20.6% in 2017. Interestingly, the smoking prevalence among females did not increase proportionally during the same period. The likely explanation may be due to increase in females seeking medical attention over the last decade, or exposure/susceptibility to other unknown risk factors. Most patients had poor educational status, with as many as 54.7% being either illiterate or educated up to primary level only. The prevalence of smoking in this series (80%) is comparable to other Indian studies, but lower than most Western data[53,72,113,114,225], which have reported smoking prevalence between 87% and 93%. This observation supports the possibility of other contributing factors in lung cancer aetiology, such as genetic predisposition, passive smoking, air pollution, and biomass fuel that is commonly used in rural India. However, the prevalence of smoking in this cohort remained largely unchanged over 10 years.

Although majority of patients in AIIMS study had a reasonably good performance status at the time of initial presentation (50.8% had Eastern Cooperative Oncology Group (ECOG) 0 or 1; and 53.3% had KPS more than 70, this was lower than most Western reports. This may be due to morbidity associated with more advanced stage of the disease at the time of diagnosis and seeking medical care. In the initial years of this study, squamous cell type dominated the morphological type of NSCLC but was overtaken by adenocarcinoma in 2012, and this trend continued till 2018. Similar to the observations made by the PGI group, the distribution of squamous cell and small cell types remained largely unchanged, the frequency of NSCLC-NOS declined. This occurred most likely due to the changing practices of pathological reporting keeping in tune with the advancement in IHC techniques and based on the revision of guidelines for pathological reporting for lung cancer. Another contributory factor may be an increase in the proportion of females over the 10-year period. Several studies, including from this group, have previously reported that adenocarcinoma has surpassed SCC as the most common histological subtype of lung cancer. This shift seems to be attributable partly to the changed smoking pattern and the increasing incidence of lung cancer in females and non-smokers. At the same time, it is worthwhile to note that most previous Indian studies have described squamous histology as the most common pathological subtype. Although bronchoscopy and transthoracic-guided sampling remain the most common diagnostic modalities for lung cancer, the past decade has seen the emergence of newer techniques, such as convex-probe EBUS, radial probe EBUS, and thoracoscopy with impressive diagnostic yield and sensitivity. Lung cancer is now being diagnosed with more and more diagnostic procedures, like fine needle aspiration, bronchoscopy, transbronchial lung biopsy (TBLB), EBUS, CT/PET guided biopsies, and thoracoscopy etc. CT scan and PET scans are now available freely. Less than 3% of their patients underwent surgery, and this probably reflects the relatively poor survival among these patients. Many of the Indian patients with lung cancer have low performance status that as been highlighted in many studies.[210-212] Although staging of lung cancer is not done very aggressively, most authors mention that lung cancer in this country presents in a very advanced stages (Tables 16 and 17).[86,105,213]

Table 16. Stage of presentation of lung cancer in India

Author[Ref]	Number of Cases	Non-Small Cell Lung Cancer								Small Cell Lung Cancer	
		7th Edition TNM Staging (%)				8th Edition TNM Staging (%)				Limited Stage (%)	Extensive Stage (%)
		I	II	III	IV	I	II	III	IV		
Mohan *et al*[105]	NSCLC 1582 SCLC 275	14 (1.2)	44 (3.8)	337 (29.1)	766 (65.9)	7 (1.6)	8 (1.9)	127 (30.2)	279 (66.3)	68 (24.8)	207 (75.2)
Kaur *et al*[86]	1301	Stage I and II–46 (3.5%); Stage IIIA–170 (13.1%); Stage IIIB–392 (30.1%); Stage IV–693 (53.3%).								125 (50)	125 (50)
NCRP[32]	23,055	Localised–14.6%; Loco-regional–35.3%; Distant metastasis–44.8%; Unknown–5.3% Loco-regional in 37.0% in males and 29.8% in females with lung cancer									

Note: 7th Edition of TNM staging by the IASLC (International Association for the Study of Lung Cancer) in 2010; and 8th Edition in 2017.

Table 17. Stage at diagnosis and relationship with smoking from PGI, Chandigarh studies[214,215]

Characteristic	Heavy Smokers (SI ≥301; n = 235)	Light/Moderate smokers (SI = 1–300; n = 150)	Never-smokers (n = 135)
Females	2.1%	12.0%	51.9%
Mean age (years)	61.2 (9.4)	58.6 (9.9)	54.5 (12.5)
SqCC	57.9%	50.0%	28.1%
KPS 90-100	63.4%	58.9%	64.6%
Stage IV NSCLC	39.1%	46.0%	67.4%
Advanced NSCLC	81.2%	80.7%	91.9%
Extra-thoracic disease	16.6%	28.0%	41.5%

All group differences (except PS) were highly statistically significant (P<0.001)

Table 15 shows various symptoms present in lung cancer patients. Rare manifestations are also described.[216] In the country, now various diagnostic modalities are widely available that includes chest radiograph, CT scan[217,218], PET scan[219], and various other invasive and semi-invasive methods.[220-250] Molecular methods are now widely available in the country[251-253] and are discussed in greater detail in the 2nd part of the review.

Management of Lung Cancer in India

Management of lung cancer has undergone major changes over the years with advancements in surgery, radiotherapy techniques, availability of newer generations of chemotherapeutic agents, and more recently the advent of molecular therapies and our understanding of immunooncology wherein immunotherapy has changed the scenario. Mortality from NSCLC decreased even faster than the incidence of this subtype, and this decrease was associated with a substantial improvement in survival over time that corresponded to the timing of approval of targeted therapy. Among men, incidence-based mortality from NSCLC decreased 6.3% annually from 2013 through 2016, whereas the incidence decreased 3.1% annually from 2008 through 2016. Corresponding lung cancer–specific survival improved from 26% among men with NSCLC that was diagnosed in 2001 to 35% among those in whom it was diagnosed in 2014. This improvement in survival was found across all races and ethnic groups. Similar patterns were found among women with NSCLC. In contrast, mortality from SCLC declined almost entirely as a result of declining incidence, with no improvement in survival.[254] CONCORD-3 survey of global surveillance of cancer survival included 37.5 million patients diagnosed with cancer during the 15-year period 2000-14. Data were provided by 322 PBCRs in 71 countries and territories, 47 of which provided data with 100% population coverage. The study includes 18 cancers or groups of cancers including lung. For most cancers, 5-year net survival remains among the highest in the world in the USA and Canada, in Australia and New Zealand, and in Finland, Iceland, Norway, and Sweden. Survival trends are generally increasing, even for some of the more lethal cancers: in some countries, survival has increased by up to 5% for cancers of the liver, pancreas, and lung. Lung cancer survival trends between 1995–1999 and 2000–2014 were generally flat, but survival increased by 5% to 10% in 21 countries. But survival was below 10% in Thailand, Brazil, Bulgaria and India[255] during this period of 15 years. The newer therapeutic approaches, particularly Stage IV NSCLC have been reviewed and recommended recently.[256,257] Like many other countries, the median survival was very poor in Indian patients with lung cancer. In earlier years in the 1980's median survival was only in weeks and with the advent of better drugs, molecular targeted therapy and immunotherapy, the situation has changed. In one of the earlier studies[258] we have shown that chemotherapy is better than best supportive care alone. As mentioned earlier, lung cancer in India is diagnosed in advanced stage of the disease. Therefore, more definite therapy, like surgery could not be offered to many and radiotherapy is only a localised form of treatment not able to take care of the distant metastatic sites. Hence, more and more patients will require systemic therapy like chemotherapy, and more recently available treatment modalities, like molecular targeted therapy and immunotherapy. However, the later two are more costly and could not be afforded by many. Many publications and experience are available in the Indian literature[259-346], both in terms of clinical experience and reviews. A detailed summary has been reviewed by Ghadyalpatil *et al*.[346]

The largest cases reported from India[105] showed that among the total 1803 patients, treatment details were available for 1013 (56.2%) patients, with the most common treatment modality being chemotherapy (87.5%) followed by radiotherapy (15.3%), targeted therapy (8.6%), and surgery (3.0%). The most common chemotherapy regimens were carboplatin-paclitaxel (53.4%), cisplatin-etoposide (18.4%), carboplatin-gemcitabine (7.4%), and carboplatin-pemetrexed (9.0%). The median overall survival was 8.8 months (IQR, 3.7–19) for all patients, and 12.6 (IQR, 6.2–28.7) months among the 1013 patients who underwent specific treatment (chemotherapy, targeted therapy, radiotherapy, or surgery) and had at least one additional follow-up visit. The remaining participants were either unwilling for chemotherapy, unsuitable due to poor performance status, opted for alternative systems of medicine, (ayurvedic or homeopathic) or were those in whom treatment details were not known. Other Indian studies have also reported a high proportion of patients unwilling or unsuitable for cancer-specific treatment for reasons similar to what was observed in one of the largest series from India.[105,202,258-261,265,267] The median overall survival in this study was similar to that reported in various other Indian studies (6.0–7.8 months), especially in advanced NSCLC. However, the overall survival of the patients who received at least some cancer-specific treatment was higher at 12.6 (6.2–28.7) months.

The NCRP of the ICMR[32] data give an idea about different management practices in the country for lung cancer (Table 18). *Practices of molecular targeted theray will be discussed in the 2nd part of the review*.

Table 18. Different management practices in India for lung cancer[32]

Extent	Localised		Loco-regional		Distant Metastasis		Unknown	
Sex	M	F	M	F	M	F	M	F
Surgery	5.8	6.9	2.1	2.3	0.6	0.6	4.6	8.6
Radiotherapy	12.4	9.6	14.3	9.3	24.2	17.4	17.0	13.3
Systemic therapy	49.0	53.3	47.6	58	42.3	50.9	48.8	55.5
Multi-modality therapy*	31.3	27.7	34	28	31.1	28.6	28.1	20.6
Palliative care	1.6	2.4	2.0	2.3	1.9	2.5	1.5	2.0

*combination of surgery and/or radiotherapy and/or chemotherapy

Figures are presented as percentage of cases

Tobacco Control in India

Tobacco use continues to be important due to the significant amount of tobacco-attributable NCDs and deaths in India and lung cancer in particular and its use continues to be a significant burden due to its magnitude and different forms of use in India.[347] The pattern and predictors of smoking, chewing, and any tobacco use among adults of age 15–49 years in India was studied using secondary data from the fourth round of the National Family and Health Survey (NFHS, 2015–2016) which collected information on tobacco use from men and women in the age group 15–49 years (n = 803,097). Bivariate and multivariate analyses were conducted to understand the socio-economic and demographic predictors. Geographic Information System (GIS) maps have been used to show inter-state variation by gender in smoking, chewing, and any tobacco use. About one out of every 10 adults aged 15–49 use any tobacco, predominantly in chewing forms. Women are significantly less likely to smoke (OR=0.05, CI=0.04–0.05), chew (OR=0.25, CI=0.24–0.25), and use any tobacco (OR=0.14, CI=0.13–0.14) compared with men. Tobacco usage was found more common among the uneducated and economically weak people. There is considerable inter-state heterogeneity in the prevalence and type of tobacco use, and adults in the north-east region are among the most vulnerable population subgroups. The higher use among males, illiterates, economically weak, socially backward and alcohol users suggest the need for targeted efforts to improve their knowledge and awareness about the harmful effects of tobacco use and stronger enforcement of tobacco control policies. The Global Adult Tobacco Survey-2 (GATS-2) in India was a household survey of 74037 persons, aged 15 or more, which was conducted in all 30 states of India and two union territories in 2016-17. As per this survey, 6% of adults aged 15 and above (267 millions) used tobacco in any form with 199 million use smokeless tobacco, 100 million smoke tobacco and 32 million smoke as well as chew tobacco.[348-350] The most commonly used tobacco products are "*khaini*" (a type of smokeless tobacco) with 85 million users and *bidi* (hand rolled cigarette) 67 million users. About 199 million users live in rural area and 68 million in urban area. Currently, 19.0% of men, 2.0% of women and 10.7% (99.5 million) of all adults smoke tobacco. The prevalence of cigarette smoking was in 7.3% in men and 0.6% in women, with an overall percentage of 4.0%. *Bidi* smoking is more common in India with *bidi* being the most common product. Whie 14.0% men and 1.2% women smoked in this country as per the survey.[347] Currently, 29.6% of men, 12.8% of women and 21.4% (199.4 million) of all adults use smokeless tobacco and 42.4% of men, 14.2% of women and 28.6% (266.8 million) of all adults currently use tobacco (smoked and/or smokeless tobacco). Current smokers (55.4%) are planning or thinking of quitting smoking and 49.6% of current smokeless tobacco users are planning or thinking of quitting smokeless tobacco use. Nearly, 48.8% of current smokers were advised by health-care providers to quit smoking and 31.7% of current smokeless tobacco users were advised by health-care providers to quit the use of smokeless tobacco. About 38.7% of adults were exposed to second-hand smoke at home, 30.2% of adults who work indoors were exposed to second-hand smoke at their workplace, 7.4% of adults were exposed to second-hand smoke at restaurants and 23% adults are still exposed to second- hand smoke at public places. 19.2% of adults noticed smoking tobacco advertisement and 18.3% of adults noticed smokeless tobacco advertisement. 68.0% of adults noticed anti-smoking tobacco information on television or radio and 59.3% of adults noticed anti-smokeless tobacco information on television or radio. 92.4% of adults believed that smoking causes serious illness and 95.6% of adults believed that use of smokeless tobacco causes serious illness. There are significant changes compared to GATS-1 with 17% relative decrease in tobacco prevalence and the tobacco use among 15-24 year olds

showed relative reduction of 33% and for 15-17 year olds, there was a 54% reduction. The age of initiation of tobacco use increased by 1 year (17.9 to 18.9). While there was a decrease in second-hand smoke exposure in public places (6%) and at home (13%), there was no decrease in workplaces. Between these two surveys, 9% (83% to 92%) more believed that second-hand smoke is harmful and 7% (89% to 96%) more believed that smokeless tobacco is harmful. However, the areas of concern are that 68% of smokers, 17% of *bidi* smokers, and 50% of smokeless tobacco users purchase loose tobacco. Nearly 10% of people still notice some form of tobacco advertisement and despite the *gutka* ban, 51 million people were still able to buy *gutka*. The 2017 National Health Policy of the Government of India had set a target of relative reduction in current tobacco use by 15% by 2020; a target which has now been exceeded. The next target is a 30% reduction by 2025.

The National Tobacco Control Programme (NTCP) of India is mainly focussed on controlling tobacco use in the country and the main aim is to bring about greater awareness about the harmful effects of tobacco use and about the Tobacco Control Laws; and also to facilitate effective implementation of the Tobacco Control Laws (COTPA 2003). India became a Party to the WHO Framework Convention on Tobacco Control on February 27, 2005. The Cigarettes and Other Tobacco Products (Prohibition of Advertisement and Regulation of Trade and Commerce, Production, Supply and Distribution) Act, 2003 (COTPA) is the principal comprehensive law governing tobacco control in India. The Act was passed before India became a Party to the WHO Framework Convention on Tobacco Control. Various laws and enactments in the country are given below.

Smoke Free Places

Smoking is completely banned in many public places and work-places, such as health-care, educational, and government facilities and on public transport. The law, however, permits the establishment of smoking areas or spaces in airports, hotels having 30 or more rooms, and restaurants having seating capacity for 30 or more. With respect to outdoor places, open auditoriums, stadiums, railway stations, bus stops/stands are smoke free. Sub-national jurisdictions may enact smoke free laws that are more stringent than the national law.

Tobacco Advertising, Promotion and Sponsorship

Advertising through most forms of mass media is prohibited. There are some restrictions on tobacco sponsorship and the publicity of such sponsorship.

Tobacco Packaging and Labelling

Health warning labels are pictorial and text; cover 85% of the front and back panels of the tobacco product package parallel to the top edge; and are rotated every 12 months. Misleading packaging and labeling, including terms such as "light," and "low-tar" and other signs, is prohibited.

Cigarette Contents and Disclosures

The law does not grant the authority to regulate the contents of cigarettes. The law does not require that manufacturers and importers disclose to government authorities information on the contents and emissions of their products.

Sales Restrictions

The law prohibits the sale of tobacco products via vending machines and within 100 yards of any educational institution. In addition, several states ban the sale of single cigarettes and *gutka* and other forms of smokeless tobacco. There are no restrictions on internet sales or the sale of small packets of cigarettes or other tobacco products. The sale of tobacco products is prohibited to persons under the age of 18 years.

E-Cigarettes

The law prohibits the production, manufacture, import, export, transport, sale, distribution, and advertising of e-cigarettes. However, there are no restrictions on the use of e-cigarettes.

This period also witnessed the emergence of new contributors outside the Ministry of Health providing additional powerful tools for tobacco control. The Ministry of Women and Child Development amended the Juvenile Justice Act to make the sale of tobacco to minors as a non-bailable offence punishable by seven years of rigorous imprisonment and a fine of up to 100,000 Indian Rupees. The Department of Consumer Affairs amended the Legal Metrology Act to prohibit sale of loose cigarettes, which currently accounts for over 70% of the country's total cigarette sales. Meanwhile, a regulation under the Food Safety Act (2011) prohibited addition of tobacco and nicotine to any food substance. Through public interest litigation, this regulation enabled the Supreme Court to order a nationwide ban on *gutka* (a combination of flavored smokeless tobacco and areca nut). In addition, more than a dozen states have independently prohibited flavoured smokeless tobacco products – an important step given *gutka* is a risk factor for oral cancers. The issue of tobabacco use in India has been highlighted by other authors also.[351-361]

To assist the country-level implementation of effective interventions to reduce the demand of

tobacco, the WHO Framework Convention on Tobacco Control introduced the MPOWER package, consisting of six policy intervention strategies: *Monitor* tobacco use and prevention policies, Protect people from tobacco smoke, Offer help to quit tobacco use, Warn about the dangers of tobacco, Enforce bans on tobacco advertising, promotion and sponsorship, and Raise taxes on tobacco.

Screening of Lung Cancer in India

Although screening for lung cancer in specific population groups is now accepted as a routine practice in many developed nations,[362-368] implementation of lung cancer screening is challenging in developing countries, even though there is an increasing trend in lung cancer incidence in these countries attributed to tobacco smoking and various environmental and occupational risk factors. So organised lung cancer screening is practically non-existent in these countries including India. There are numerous challenges in implementing such programmes ranging from infrastructure, trained human resources, referral algorithm to cost and psychological trauma due to over-diagnosis. Pulmonary TB and other chest infections are important issues to be addressed while planning for lung cancer screening in the developing countries. Burden of these diseases is very high and can lead to over-diagnosis in view of cut-off of lung nodule size in various studies. Assessment of high risk cases for lung cancer is difficult as various forms of smoking make quantification non-uniform and difficult. Lung cancer screening targets only high risk population unlike screening programmes for other cancers where entire population is targeted. There is a need for lung cancer screening for high risk cases as it saves lives. Tobacco control and smoking cessation remain the most important long-term intervention to decrease morbidity and mortality from lung cancer in the developing countries. There is no sufficient evidence supporting the introduction of population-based screening for lung cancer in public health services.[369-376] However, many centres do the screening programme like the Dharamshila Narayana Superspeciality Hospital (A Unit of Dharamshila Cancer Foundation and Research Centre), New Delhi and others. Through this programme, the center provides low-dose CT screening for people who were between the ages of 55 and 74, and have smoked 30 or more pack years. (This is the number of years smoked multiplied by the number of packs of cigarettes smoked per day, *e.g.* one pack per day for 30 years equals 30 pack years.)

Most countries or organisations have not framed any guidelines for lung cancer screening due to cost effectiveness and morbidity issues related to low-dose computed tomography (LDCT). Various methods have been tried, such as chest radiography, sputum cytology; however, low dose computed tomography has been shown to be an effective screening modality for lung cancer. Along with an overall increase in the incidence, there is a rapid increase amongst non-smokers and women. The patients are being seen at younger and younger age group. While smoking continues to be the primary cause, extremely high air pollution levels are a possible contributory factor for exponential rise in the incidence of lung cancer in non-smoking population. Another screening trial is being studied at the PGIMER, Chandigarh where 200 individuals aged 55-74 years with at least 30 pack-year history of smoking (or smoking index ≥600) who are current smokers or quit within the last 15 years or individuals aged 50-74 years with at least 20 pack-year history of smoking (or smoking index ≥400) who are current or former smokers with COPD or family history of lung cancer in any first-degree relatives.[376]

Amongst the various methods for early detection, the only one that has proven to reduce the lung cancer mortality is the "Low Dose Computed Tomographic Screening" as demonstrated in the "National Lung Cancer Screening Trial (NLST)". The NLST showed that a LDCT screen followed by two annual screens, compared to standard lung x-ray screening, reduced the lung cancer mortality by 20% and overall mortality by 7% over a 6-year follow-up period in individuals at high-risk for developing lung cancer. Despite such promising outcomes, the results have to be analysed with care, particularly from the Indian perspective. The NLST demonstrated a reduction in mortality, but with high false positive rates mostly attributed to benign infective lesions. That raises serious concerns regarding its usefulness in countries with TB as a widely prevalent endemic problem. However, there have been no studies from India which actually evaluate the feasibility of LDCT in early diagnosis of lung cancer.

COVID and Lung Cancer

While all types of malignancies seem to be associated with high COVID-19 prevalence, morbidity and mortality, lung cancer represents a specific scenario of cumulative risk factors for COVID-19 complications, including older age, significant cardiovascular and respiratory co-morbidities, smoking-related lung damage, as well as the unavoidable addition of treatment-related immune impairment or suppression.[377] In a retrospective analysis of 1524 patients with cancer, it is reported and highlighted that patients with cancer harboured a higher risk of SARS-CoV-2 infection (OR=2.31; 95% CI=1.89 to 3.02)

compared to the general population. This risk appears increased in both patients with or without active anti-cancer treatments. The most likely to develop COVID-19 were patients with NSCLC and above the age of 60.[378] Subsequently, there are many other studies which describe various aspects of lung cancer during COVID-19 pandemic.[379-387] In India also management issues during the pandemic have been discussed by various authors.[388-390]

References

1. History of Cancer. 19th Century. *The Cancer Atlas. Available from URL:* canceratlas.cancer.org history-cancer. Accessed on October 11, 2020.
2. American Cancer Society. The History of Cancer. *First Cancer Diagnosis. Available from URL:* http://www.cancer.org cancer history-of-cancer. Accessed on October 11, 2020.
3. Nath V, Grewal KS. Cancer in India. *Indian J Med Res* 1935;23:149–90.
4. Behera D, Balamugesh T. Lung cancer in India. *Indian J Chest Dis Allied Sci* 2004;46:269–81.
5. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396:1204–22.
6. World Health Organization. *Global Health Observatory*. Geneva: World Health Organization; 2018. *Available from URL:* who.int/gho/database/en/. Accessed on October 10, 2020.
7. World Health Organization. Global health estimates 2016: deaths by cause, age, sex, by country and by region, 2000-2016. *Human Development Report 2016*. Geneva: World Health Organization; 2018.
8. American Cancer Society. *Global Cancer Facts and Figures*. 4th edition. Atlanta: American Cancer Society; 2018.
9. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424.
10. World Health Organization. Setting priorities, investing wisely and providing care for all. *WHO Report on Cancer*. Geneva: World Health Organization; 2020.
11. https://canceratlas.cancer.org/wp-content/uploads/2019/09/CA3_LungCancer.pdf. Accessed on October 11, 2020.
12. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.
13. National Cancer Institute, USA, 2020. Accessed on October 13, 2020.
14. Varlotto JM, Voland R, McKie K, Flickinger JC, DeCamp MM, Maddox D, *et al.* Population-based differences in the outcome and presentation of lung cancer patients based upon racial, histologic, and economic factors in all lung patients and those with metastatic disease. *Cancer Med* 2018;7:1211–20.
15. Lu T, Yang X, Huang Y, Zhao M, Li M, Ma K, *et al.* Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. *Can Manage Res* 2019:11 943–53.
16. Centers for Disease Control and Prevention (CDC), the North American Association of Central Cancer Registries (NAACCR), the American Cancer Society (ACS), and the National Cancer Institute (NCI). *Annual Report to the Nation on the Status of Cancer*. National Cancer Institute, The Surveilance, Epidemiology, and End Result Program; 2020.
17. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, *et al*. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 2018;103:356–87.
18. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, *et al.* the EUROCARE-5 Working Group. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5: a population-based study. *Lancet Oncol* 2014;5:23–34.
19. ECIS - European Cancer Information System. *ECIS Contributing Initiatives and Studies.* Accessed on October 13, 2020.
20. Shin H, Clem M Carlos, Varghese C. Cancer control in the Asia Pacific region: current status and concerns. *Japan J Clin Oncol* 2012;42:867–81.
21. Sekine I, Shintani Y, Shukuya T, Takayama K, Inoue A, Okamoto I, *et al*. A Japanese lung cancer registry study on demographics and treatment modalities in medically treated patients. *Cancer Sci* 2020;111:1685–91.
22. Global Cancer Observatory, International Agency for Research on Cancer, WHO. Cancer burden in Japan. *GLOBOCAN*, 2018. Accessed on October 12, 2020.
23. Cao M, Li H, Sun D, Chen W. Cancer burden of major cancers in China: a need for sustainable actions. *Cancer Communic* 2020;40:205–21.
24. Gao S, Li N, Wang S, Zhang F, Wei W, Li N, *et al*. Lung cancer in People's Republic of China. *J Thorac Oncol* 2020;15:1567–76.
25. Behera D. Epidemiology of lung cancer: Global and Indian perspective. *J Indian Acad Clin Med* 2012;13:131–7.
26. Noronha V, Dikshit R, Raut N, Joshi A, Pramesh CS, George K, *et al*. Epidemiology of lung cancer in India: focus on the differences between non-smokers and smokers: a single-centre experience. *Indian J Cancer* 2012;49:74–81.
27. Parikh PM, Ranade AA, Govind B, Ghadyalpatil N, Singh R, Bharath R, *et al*. Lung cancer in India: current status and promising strategies. *South Asian J Cancer* 2016;5:93–95.
28. Dubey AK, Gupta U, Jain S. Epidemiology of lung cancer and approaches for its prediction: a systematic review and analysis. *Chinese J Cancer* 2016;35:71–83.
29. Noronha V, Pinninti R, Patil VM, Joshi A, Prabhash K. Lung cancer in the Indian subcontinent. *South Asian J Cancer* 2016;5:95–103.

30. Behera D. Lung cancer in India: challenges and perspectives. *J Thorac Oncol* 2017;12:S114.
31. Behera D, Maturu VN. Lung cancer. In: Droz JP, Carme B, Couppié P, Nacher M, Thiéblemont C, editors *Tropical Hemato-Oncology*. Springer: Cham. *Available from URL:* https://doi.org/10.1007/978-3-319-18257-5_37; 2015;363–72. Accessed on October 10, 2020.
32. National Centre for Disease Informatics and Research. National Cancer Registry Programme. *Report of National Cancer Registry Programme* (2012-2016). Bengaluru, India: Indian Council of Medical Research; 2020.
33. Dar MA, Sharma KK. Burden of cancer in India: Globocan 2018 estimates. Incidence, mortality, prevalence, and future projections of cancer in India. *J Emerg Technol Invat Res* 2019;6:505–14.
34. India State-Level Disease Burden Initiative Cancer Collaborators. The burden of cancers and their variations across the states of India: the Global Burden of Disease Study 1990–2016. *Lancet Oncol* 2018;19:1289–1306.
35. Chandramohan K, Thomas B. Cancer trends and burden in India. *Lancet Oncol* 2018;19:E663.
36. Viswanathan R, Gupta S, Iyer PVK. Incidence of primary lung cancer in India. *Thorax* 1962;17:73–76.
37. Wig KL, Lazaro EJ, Gadekar NG, Guleria JS. Bronchogenic carcinoma: clinical features and diagnosis. *Indian J Chest Dis* 1961;3:209–18.
38. Basu BK, Ghosh TN. A study of bronchogenic carcinoma. *Indian J Chest Dis* 1971;13:1–9.
39. Sinha BC. Lung cancer: clinical features. *Indian J Chest Dis* 1961;3:209–18.
40. Karai GS, Nath HK, Paul G, Saha D, Roy HK. Carcinoma of the lung: a record and analysis of 100 cases. *Indian J Cancer* 1967;4:105–13.
41. Shankar PS. Bronchogenic carcinoma. *Indian J Chest Dis* 1967;9:161–4.
42. Nagrath SP, Hazra DK, Lahiri B, Kishore B, Kumar R. Primary carcinoma of the lung: clinicopathological study of 35 cases. *Indian J Chest Dis* 1970;12:15–24.
43. Reddy, DB, Prasanthamurthy D, Satyavathi S. Bronchogenic carcinoma: a clinico-pathological study. *Indian J Chest Dis* 1972;14:86–89.
44. Guleria JS, Gopinath N, Talwar JR, Bhargava S, Pande JN, Gupta RG. Bronchial carcinoma: an analysis of 120 cases. *J Assoc Physicians India* 1971;19:251–5.
45. Jha VK, Roy DC, Ravindran P. Bronchogenic carcinoma: a clinicopathological study. *Indian J Chest Dis* 1972;14:78–85.
46. Nafae A, Misra SP, Dhar SN, Shah SNA. Bronchogenic carcinoma in Kashmir valley. *Indian J Chest Dis* 1973;15:285–95.
47. Malik AK, Aikat BK. Primary pulmonary neoplasm: a histopathologic study. *Indian J Cancer* 1976;13:149–55.
48. Narang RK, Dubey AL, Gupta MC, Raju S. Primary bronchial carcinoma: a clinical study. *Indian J Chest Dis Allied Sci* 1977;19:120–23.
49. Jindal SK, Malik SK, Malik AK, Singh K, Gujral JS, Sodhi JS. Bronchogenic carcinoma: a review of 150 cases. *Indian J Chest Dis Allied Sci* 1979;21:59–64.
50. Notani P, Sanghavi LD. A retrospective study of lung cancer in Bombay. *Br J Cancer* 1974;29:477–82.
51. Garg UK, Srivastava VK, Rajwanshi VS, Maheshwari BB. Carcinoma of lung: a correlative cytological and histopathological study. *Indian J Cancer* 1973;10:204–11.
52. Malhotra V, Malik R, Beohar PC, Gondal R, Khanna SK, Narayanan PS. Tumours of the lung: histomorphological study. *Indian J Chest Dis Allied Sci* 1986;28:28–40.
53. Jindal SK, Behera D. Clinical spectrum of primary lung cancer: review of Chandigarh experience of 10 years. *Lung India* 1990;8:94–98.
54. Arora VK, Seetharaman ML, Ramkumar S, Mamatha TV, Subbarao KSVK, Banerjee A, *et al.* Bronchogenic carcinoma: clinicopathological patten in south Indian population. *Lung India* 1990;7:133–8.
55. Rao S, Rau PVP, Sahoo RC. Bronchogenic carcinoma in the young. *Lung India* 1992;10:101–2.
56. Rajasekaran S, Manickam TG, Vasanthan PJ, *et al.* Pattern of primary lung cancer: a Madras study. *Lung India* 1993;9:7–11.
57. Gupta RC, Purohit SD, Sharma MP, Bhardwaj S. Primary bronchogenic carcinoma: clinical profile of 279 cases from mid-west Rajasthan. *Indian J Chest Dis Allied Sci* 1998;40:109–16.
58. Thippanna G, Venu K, Gopalkrishnaiah V, Reddy PNS, Sai Charan BG. A profile of lung cancer patients in Hyderabad. *J Indian Med Assoc* 1999;97:357–9.
59. Arora VK, Sharma V, Reddy KS. Bronchogenic carcinoma in patients below age 40 years and the response to radiotherapy with or without CMF regime. *Lung India* 1998;16:155–8.
60. Gupta D, Boffetta P, Gaborieau V, Jindal SK. Risk factors of lung cancer in Chandigarh, *India. Indian J Med Res* 2001;113:142–50.
61. Kashyap S, Mohapatra PR, Negi RS. Pattern of primary lung cancer among bidi smokers in North-Western Himalayan region of India. *Lung Cancer* 2003;41 (Suppl. 2):S111.
62. Prasad R, James P, Kesarwani V, Gupta R, Pant MC, Chaturvedi A, *et al.* Clinicopathological study of bronchogenic carcinoma. *Respirology* 2004;9:557–60.
63. Khan NA, Afroz F, Lone M, Teli M, Muzaffar M, Jan N. Profile of lung cancer in Kashmir, India: a five-year study. *Indian J Chest Dis All Sci* 2006;48:187–90.
64. Rawat J, Sindhwani G, Gaur D, Dua R, Saini S. Clinico-pathological profile of lung cancer in Uttarakhand. *Lung India* 2009;26:74–76.
65. Prasad R, Verma SK, Sanjay. Comparison between young and old patients with bronchogenic carcinoma. *J Cancer Res Ther* 2009;5:31–35.
66. Koul PA, Kaul SK, Sheikh MM, Tasleem RA, Shah A. Lung cancer in the Kashmir valley. *Lung India* 2010;27:131–7.
67. Sheikh S, Azra S, Aijaz A, Makhdoomi R, Rais A. Histological pattern of primary malignant lung tumours diagnosed in a tertiary care hospital: 10 year study. *Asian Pac J Cancer Pre* 2010;11:1341–6.

68. Bhattacharyya SK, Mandal A, Deoghuria D, Agarwala A, Ghoshal AG, Dey SK. Clinico-pathological profile of lung cancer in a tertiary medical centre in India: analysis of 266 cases. *J Dentistry Oral Hygiene* 2011;3:30–33.
69. Dey A, Biswas D, Saha SK, Kundu S, Kundu S, Sengupta A. Comparison study of clinicoradiological profile of primary lung cancer cases: an Eastern India experience. *Indian J Cancer* 2012;49:89–95.
70. Noronha V, Dikshit R, Raut N, Joshi A, Pramesh CS, George K, *et al*. Epidemiology of lung cancer in India: focus on the differences between non-smokers and smokers: a single-centre experience. *Indian J Cancer* 2012;49:74–81.
71. Bhaskarapillai B, Kumar SS, Balasubramanian S. Lung cancer in Malabar Cancer Center in Kerala: a descriptive analysis. *Asian Pac J Cancer Prev* 2012;13:4639–43.
72. Mandal SK, Singh TT, Sharma TD, Amrithalingam V. Clinico-pathology of lung cancer in a regional cancer center in Northeastern India. *Asian Pac J Cancer Prev* 2013;14:7277–81.
73. Malik PS, Sharma MC, Mohanti BK, Shukla NK, Deo S, Mohan A, *et al*. Clinico-pathological profile of lung cancer at AIIMS: a changing paradigm in India. *Asian Pac J Cancer Prev* 2013;14:489–94.
74. Sundaram V, Sanyal N. Clinicopathological profile of bronchogenic carcinoma in a tertiary care hospital in eastern part of India. *Clin Cancer Investig J* 2014;3:220–4.
75. Yogeesha KS, Vijayamahantesh NN, Raghavendra Bakki Sannegowda. Clinical presentation of lung cancer in adults: a retrospective study of 61 patients from a teritiary care centre in south India. *Intern J Basic Appl Med Sci* 2014;4:195–7.
76. Dubey N, Julka A, Varudkar HG, Agrawat JC, Bhandari D, Mukati S, *et al*. A clinico-pathological profile of primary lung cancer patients presenting in a rural medical college of Central India. *Panacea J Med Sci* 2015;5:124–9.
77. Pandhi N, Malhotra B, Kajal NC, Prabhudesai RR, Nagaraja CL, Mahajan N. Clinicopathological profile of patients with lung cancer visiting chest and TB hospital Amritsar. *Sch J App Med Sci* 2015;3:802–9.
78. Baburao A, Narayanswamy H. Clinico-pathological profile and haematological abnormalities associated with lung cancer in Bangalore, India. *Asian Pac J Can Prev* 2016;16:8235–8.
79. Dhandapani S, Srinivasan A, Rajagopalan R, Chellamuthu S, Rajkumar A, Palaniswamy P. Clinicopathological profile of lung cancer patients in a teaching hospital in South India. *J Cardiothorac Med* 2016;4:440–3.
80. Pujari VV, Lokhande RM, Meshram SH, Waghmore RD. Clinical and pathological presentations of bronchogenic carcinoma in a tertiary care centre. *J Evolution Med Dent Sci* 2016;5:3068–71.
81. Bhadke B, Rathod RK, Deshmukh DG, Luniya AB, Mahajan P, Surjushe AU. Clinical profile of lung cancer in rural medical college of Maharashtra (India): a prospective study of three years. *Int J Med Res Rev* 2016;4:1063–71.
82. Kumar M, Sharma DK, Garg M, Jain P. Clinicopathological profile of lung cancer: changing trends in India. *Int J Res Med* 2016;5:57–62.
83. Kshetrimayum S, Srivastava A, Kant S, Verma A, Ved P, Bajaj D, *et al*. A study of the sociodemographic, clinical, pathological and radiological profile of lung cancer in a tertiary care center. *Int J Adv Med* 2016;3:920–7.
84. Neliyathodi S, Krishnan a, Gopinath D. Clinical radiological and immunohistochemical profile of non small cell lung carcinoma. *South Am J Med* 2016;4:1–12.
85. Mohan A, Latifi AN, Guleria R. Increasing incidence of adenocarcinoma lung in India: following the global trend? *Indian J Cancer* 2016;53:92–5.
86. Kaur H, Sehgal IS, Bal A, Gupta N, Behera D, Das A, *et al*. Evolving epidemiology of lung cancer in India: reducing non-small cell lung cancer-not otherwise specified and quantifying tobacco smoke exposure are the key. *Indian J Cancer* 2017;54:285–90.
87. Nair CK, Mathew AP, George PS. Lung cancer: presentation and pattern of care in a cancer center in South India. *Indian J Cancer* 2017;54:164–8.
88. Singh R, Rohtagi N. Clinicopathological and molecular epidemiological study of lung cancer patients seen at a tertiary care hospital in Northern India. *South Asian J Cancer* 2017;6:171–5.
89. Sreekala C, Kumari KA, Jayaprakash B. Epidemiological pattern of lung cancer in a tertiary care centre: a prospective observational study. *Int J Med Res Rev* [Internet] 2017;5:839–44.
90. Sharma T, Ghewade B, Jadhav U, Chaudhari S. Clinical profile of lung cancer at Acharya Vinoba Bhave Rural Hospital. *J Datta Meghe Inst Med Sci Univ* 2017;12:41–4.
91. Vasu PP, Sujatha D, Leelamma JP. Clinical and cytomorphological evaluation of primary lung neoplasms in a tertiary care teaching centre of south India. *J Evolution Med Dent Sci* 2017;6:3240–5.
92. Lakshmaiah KC, Kamath MP, Babu KG, Amirtham U, Loknatha D, Komaranchath AS. Metastatic nonsmall cell lung cancer in South India: a regional demographic study. *Indian J Cancer* 2017;54:267–70.
93. George KC, TM A, Nambiar RK. Clinical, epidemiological and diagnostic profile of patients with carcinoma lung: a clinical study. *J App Med Sci* 2017;5:3714–8.
94. Soman R, Govindaraj V, Saka V, Badhe B, Dubashi B. Clinico-pathological profile of primary lung cancer in a tertiary care center in South India. *Indian J Immunol Respir Med* 2018;3:165–9.
95. Agrawal A, Tandon R, Singh L, Kumar P, Pant H, Prakash S. Clinical profile of lung cancer in a tertiary care teaching hospital in north India with special reference to acceptance and outcome of treatment. *J Pulmon* 2018;2:4–8.
96. Sarfraz S, Gupta R, Bhardwaj S. Histopathological patterns of endobronchial lung biopsy specimen in lung cancer along with clinico-radiological correlation. *Int J Contempor Med Res* 2018;5:K1–K5.

97. Dattatreya SP, Bansal R, Vamsy M, Vaniawala S, Nirni SS, Dayal M, *et al.* Clinicopathological profile of lung cancer at a tertiary care center. *Indian J Cancer* 2018;55:273–5.
98. Thakkar D, Damor PK, Vithalani K. Clinicopathological profile of patients with bronchogenic carcinoma at a tertiary care center in Western India. *Indian J Respir Care* 2019;8:80–83.
99. Pandey A, Raj S, Madhawi R, Devi S, Singh RK. Cancer trends in Eastern India: retrospective hospital-based cancer registry data analysis. *South Asian J Cancer* 2019;8:215–7.
100. Ahmad DS, Waheed DA, Ahmad SS, Sunaullah K, Haneefa A, Subiya K, *et al.* A study of the sociodemographic, clinical and pathological profile of lung cancer: a study conducted at Government Medical College Srinagar, Kashmir, India. *Int J Adv Res* 2019;7:937–40.
101. Raghavendra C, Gupta GRK, Reddy VVR. Clinico-pathological profile of primary lung cancer in a tertiary care teaching hospital in the south-east coast of India. *Indian J Immunol Respir Med* 2019;4:205–9.
102. Premananth P, Gnanasekaran R, Nagarajan N, Deiveegan. Lung cancer profile at tertiary care hospital, South Tamilnadu. *Indian J Immunol Respir Med* 2019;4:245–51.
103. Gaur P, Bhattacharya S, Kant S, Kushwaha RA, Garg R, Pandey S, *et al*. Hospital-based study on demographic, hematological, and biochemical profile of lung cancer patients. *J Cancer Res Ther* 2020;16:839–42.
104. Darling HS, Viswanath S, Singh R, Ranjan S, Pathi N, Rathore A, *et al*. A clinico-epidemiological, pathological, and molecular study of lung cancer in North-western India. *J Can Res Ther* 2020;16:771–9
105. Mohan A, Garg A, Gupta A, Sahu S, Choudhari C, Vashistha V, *et al*. Clinical profile of lung cancer in North India: a 10-year analysis of 1862 patients from a tertiary care center. *Lung India* 2020;37:190–7.
106. Parikh PM, Ranade AA, Govind B, Ghadyalpatil N, Singh R, Bharath R, *et al.* Lung cancer in India: current status and promising strategies. *South Asian J Cancer* 2016;5:93–5.
107. Noronha V, Pinninti R, Patil VM, Joshi A, Prabhash K. Lung cancer in the Indian subcontinent. *South Asian J Cancer* 2016;5:95–103.
108. Shankar A, Dubey A, Saini D, Singh M, Prasad CP, Roy S, *et al*. Environmental and occupational determinants of lung cancer. *Transl Lung Cancer Res* 2019;8 (Suppl. 1):S31–S49.
109. D'Souza ND, Murthy NS, Aras RY. Projection of cancer incident cases for India–till 2026. *Asian Pac J Cancer Prev* 2013;14:4379–86.
110. D'Souza ND, Murthy NS, Aras RY. Projection of burden of cancer mortality for India, 2011-2026. *Asian Pac J Cancer Prev* 2013;14:4387–92.
111. Mohan S, Asthana S, Labani S, Popli G. Cancer trends in India: a review of population-based cancer registries (2005-2014). *Indian J Public Health* 2018;62:221–3.
112. Krishnamurthy A, Vijayalakshmi R, Gadigi V, Ranganathan R, Sagar TG. The relevance of "nonsmoking-associated lung cancer" in India: a single-centre experience. *Indian J Cancer* 2012;49:82–8.
113. Singh N, Behera D. Lung cancer epidemiology and clinical profile in North India: similarities and differences with other geographical regions of India. *Indian J Cancer* 2013;50:291.
114. Singh N, Aggarwal AN, Gupta D, Behera D, Jindal SK. Unchanging clinico-epidemiological profile of lung cancer in north India over three decades. *Cancer Epidemiol* 2010;34:101–4.
115. Jindal SK, Malik SK, Dhand R, Gujral JS, Malik AK, Datta BN. Bronchogenic carcinoma in Northern India. *Thorax* 1982;37:343–7.
116. Singh N, Aggarwal AN, Gupta D, Behera D, Jindal SK. Quantified smoking status and non-small cell lung cancer stage at presentation: analysis of a North Indian cohort and a systematic review of literature. *J Thorac Dis* 2012;4:474–84.
117. Singh N, Aggarwal AN, Gupta D, Behera D. Prevalence of low body mass index among newly diagnosed lung cancer patients in North India and its association with smoking status. *Thoracic Cancer* 2011;2:27–31.
118. Jindal SK, Aggarwal AN, Chaudhry K, Chhabra SK, D'Souza GA, Gupta D, *et al*. Tobacco smoking in India: prevalence, quit-rates and respiratory morbidity. *Indian J Chest Dis Allied Sci* 2006;48:37–42.
119. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, *et al*. ICMR-NCDIR-NCRP Investigator Group. Cancer statistics, 2020: report from National Cancer Registry programme, India. *J Glob Oncol* 2020;6:1063–75. doi: 10.1200/GO.20.00122. PMID: 32673076; PMCID: PMC7392737.
120. Sarkar S, Datta D, Debbarma S, Majumdar G, Mandal SS. Patterns of cancer incidence and mortality in North-Eastern India: the first report from the population based cancer registry of tripura. *Asian Pac J Cancer Prev* 2020;21:2493–9.
121. Smith RD, Mallath MK. History of the growing burden of cancer in India: from antiquity to the 21st Century. *J Glob Oncol* 2019;5:1–15.
122. Gharpure PV. The incidence of primary carcinoma in India as inferred from post-mortem records of fifty years from 1877 to 1926. *Indian Med Gaz* 1927;62:315–7.
123. Gharpure PV. Pathological evidence bearing on the incidence of diseases in Bombay. *Indian Med Gaz* 1928;63:253–9.
124. Gharpure PV. Incidence of primary carcinoma of the liver and other organs as inferred from autopsy work, 1926 to 1946. *Indian Med Gaz* 1948;83:5–6.
125. Mitra S, Dasgupta A. An estimate of the prevalence of cancer in India. *Bull World Hlth Organ* 1960;22:485–2.
126. Vincent RG, Pickren JW, Lane WW, Bross I, Takita H, Houten L, *et al*. The changing histopathology of lung cancer: a review of 1682 cases. *Cancer* 1977;39:1647–55.
127. Lu T, Yang X, Huang Y, Zhao M, Li M, Ma K, *et al*. Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. *Cancer Manage Res* 2019;11:943–53.

128. Loeb LA, Emster VL, Warner KE, Abbotts J, Laszlo J. Smoking and lung cancer: an overview. *Cancer Res* 1984;44:5940–58.
129. Cornfield J, Haenszel W, Hammond EC, Lilienfeld AM, Shimkin MB, Wynder EL. Smoking and lung cancer: recent evidence and a discussion of some questions. *J Natnl Canst* 1959;22:173–203.
130. Keeffe LM, Taylor G, Huxley RR, Mitchell P, Woodward M, Peters SAE. Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis. *BMJ Open* 2018;8:e021611. doi: 10.1136/bmjopen-2018-021611.
131. Bade BC, Cruz CSD. Lung cancer 2020: epidemiology, etiology, and prevention. *Clin Chest Med* 2020;41:1–24.
132. Notani P, Sanghavi LD. A retrospective study of lung cancer in Bombay. *Br J Cancer* 1974;29:477–82.
133. Jussawala DJ, Jain DK. Lung cancer in greater Bombay correlation with religion and smoking habits. *Br J Cancer* 1979;40:437–48.
134. Pakhale SS, Jayant K, Bhide SV. Methods of reduction of harmful constituents in bidi smoke. *Indian J Chest Dis Allied Sci* 1985;27:148–52.
135. Prasad R, Ahuja RC, Singhal S, Srivastava AN, James P, Kesarwani V, *et al*. A case-control study of bidi smoking and bronchogenic carcinoma. *Ann Thorac Med* 2010;5:238–41.
136. Gupta D, Boffetta P, Gaborieau V, Jindal SK. Risk factors of lung cancer in Chandigarh, India. *Indian J Med Res* 2001;113:142–50.
137. Gajalakshmi V, Hung RJ, Mathew A, Varghese C, Brennan PK. Tobacco smoking and chewing, alcohol drinking and lung cancer risk among men in southern India. *Int J Cancer* 2003;107:441–7.
138. Notani PN, Rao DN, Sirsat MV, Sanghvi LD. A study of lung cancer in relation to bidi smoking in different religious communities in Bombay. *Indian J Cancer* 1977;14:115–21.
139. Jayalekshmy PA, Akiba S, Madhavan MK, Gangadharan P, Rajan P, Nair RK, *et al.* Bidi smoking and lung cancer incidence among males in Karunagappally cohort in Kerala, India. *Int J Cancer* 2008;123:1390–7.
140. Koul PA, Hajni MR, Sheikh MA, Khan UH, Shah A, Khan Y, *et al*. Hookah smoking and lung cancer in the Kashmir valley of the Indian subcontinent. *Asian Pac J Cancer Prev* 2011;12:519–24.
141. Zhong L, Goldberg MS, Parent ME, Hanley JA. Exposure to environmental tobacco smoke and the risk of lung cancer: a meta-analysis. *Lung Cancer* 2000;27:3–18.
142. Sun S, Schiller J, Gazda, A. Lung cancer in never smokers: a different disease. *Nat Rev Cancer* 2007;7:778–90.
143. Subramanian J, Govindan R. Lung cancer in never smokers: a review. *J Clin Oncol* 2007;25: 561–70.
144. Couraud S, Zalcman G, Milleron B, Morin F, Souquet P. Lung cancer in never smokers: a review *Eur J Cancer* 2012;48:1299–11.
145. Rapiti E, Jindal SK, Gupta D, Boffetta P. Passive smoking and lung cancer in Chandigarh, India. *Lung Cancer* 1999;23:183–9.
146. Behera D, Balamugesh T. Indoor air pollution as a risk factor for lung cancer in women. *J Assoc Physicians India* 2005;53:190–2.
147. Torres-Duque C, Maldonado D, Pe´rez-Padilla R, Ezzati M, Viegi G, on behalf of the Forum of International Respiratory Societies (FIRS) Task Force on Health Effects of Biomass. Biomass fuels and respiratory diseases: a review of the evidence. *Proc Am Thorac Soc* 2008;5:577–90.
148. Kurmi OP, Lam KBH, Ayres JG. Indoor air pollution and the lung in low- and medium-income countries. *Eur Respir J* 2012;40:239–54.
149. World Health Organization. Household air pollution and health. *Available from URL:* https://www.who.int/news-room/fact-sheets/detail/household-air-pollution-and-health. Accessed on May 6, 2021.
150. Kumar R. Air pollution and respiratory health. *J Adv Pediatr Child Health* 2020;3:032–7.
151. Wong IC, Ng YK, Lui VW. Cancers of the lung, head and neck on the rise: perspectives on the genotoxicity of air pollution. *Chinese J Cancer* 2014;33:476–80.
152. Turner MC, Andersen ZJ, Baccarelli A, Diver WR, Gapstur SM, Pope A, *et al*. Outdoor air pollution and cancer: an overview of the current evidence and public health recommendations. *CA Cancer J Clin* 2020;70:460–79.
153. Christiani DC. Occupational exposures and lung cancer. *Am J Respir Crit Care Med* 2020;202:317–9.
154. Hagedoorn P, Vandenheede H, Willaert D, Vanthomme K, Gadeyne S. Regional inequalities in lung cancer mortality in Belgium at the beginning of the 21st Century: the contribution of individual and area-level socioeconomic status and industrial exposure. *PLoS One* 2016;11:e0147099.
155. Barrera-Rodriguez R, Morales-Fuentes J. Lung cancer in women. *Lung Cancer* (Auckland) 2012;3:79–89. doi:10.2147/LCTT.S37319.
156. Domagala-Kulawik J, Trojnar A. Lung cancer in women in 21th century. *J Thorac Dis* 2020;12:4398–4410.
157. Trojnar A, Domagała-Kulawik J. Lung cancer in women: is gynecological and obstetrical history important? *Oncol Clin Pract* 2021;17: DOI: 10.5603/OCP.2021.2021.0004.
158. Slebos RJ, Rodenhuis S. The molecular genetics of human lung cancer. *Eur Respir J* 1989;2:461–9.
159. Rom WN, , Hay JG, Lee TC, y Jiang Y, Tchou-Wong K. Molecular and genetic aspects of lung cancer. *Am J Respir Crit Care Med* 2000;161:1355–67.
160. Wang J, Liu Q, Yuan S, Xie W, Liu Y, Xiang Y, *et al*. Genetic predisposition to lung cancer: comprehensive literature integration, meta-analysis, and multiple evidence assessment of candidate-gene association studies. *Sci Rep* 2017;7:8371. https://doi.org/10.1038/s41598-017-07737-0.
161. Mir S, Radhika S, Wali A, Majumdar S, Joshi K, Behera D. Expression of p53 protein and the apoptotic regulatory molecules Bcl-2, Bcl-XL and Bax in locally advanced

squamous cell carcinoma of the lung. *Lung Cancer* 2004;45:181–8.

162. Wali A, Srinivasan R, Shabnam MS, Majumdar S, Joshi K, Behera D. Loss of fragile histidine triad gene expression in advanced lung cancer is consequent to allelic loss at 3p14 locus and promoter methylation. *Mol Cancer Res* 2006;4:93–99.
163. Malhotra P, Behera D, Srinivasan R, Majumdar S, Wali A, Mir S, *et al.* Detection of microsatellite alterations in bronchial washings in squamous cell lung cancer: the first study from India. *Japanese J Clin Oncol* 2004;34:439–44.
164. Mehta S, Chhetra R, Srinivasan R, Sharma SC, Behera D, Ghosh S. Detection of disease specific sialoglycoconjugate specific antibodies in bronchoalveolar lavage fluid of non-small cell lung cancer patients. *Glycocon J* 2010;27:491–500.
165. Singh N, Mootha VK, Madan K, Aggarwal AN, Behera D. Tumor cavitation among lung cancer patients receiving first-line chemotherapy at a tertiary care centre in India: association with histology and overall survival. *Med Oncol* 2013;30:602. doi: 10.1007/s12032-013-0602-z.
166. Behera D. FHIT gene expression in lung cancer cell-lines and evaluation of its effects with chemotherapeutic agents on apoptosis. *J Thorac Oncol* 2007;2(Suppl. 4):S482.
167. Pasrija T, Srinivasan R, Behera D, Majumdar S. Telomerase activity in sputum and telomerase and its components in biopsies of advanced lung cancer. *Eur J Cancer* 2007;43:1476–82.
168. Mehta S, Chhetra R, Srinivasan R, Sharma SC, Behera D, Ghosh S. Potential importance of Maackia amurensis agglutinin in non-small cell lung cancer. *Biol Chem* 2013;394:889–900.
169. Kamath A, Joseph AM, Gupta K, Behera D, Jaiswal A, Dewan R, *et al.* Proteomic analysis of HEK293 cells expressing non small cell lung carcinoma associated epidermal growth factor receptor variants reveals induction of heat shock response. *Exp Hematol Oncol* 2015;4:16.
170. Sodhi KK, Bahl C, Singh N, Behera D, Sharma S. Functional genetic variants in pre-miR-146a and 196a2 genes are associated with risk of lung cancer in North Indians. *Future Oncol* 2015;11:2159–73.
171. Singh N, Bansal R, Behera D, Gupta A. Intravitreal bevacizumab for choroidal metastases: the key to efficacy is simultaneous administration of systemic therapy. *Eye* 2015;29:1629.
172. Mehta S, Chhetra R, Srinivasan R, Sharma SC, Behera D, Ghosh S. *Corrigendum to:* Potential importance of Maackia amurensis agglutinin in non-small cell lung cancer. *Biol chem* 2015;396:1377–8.
173. Sharma N, Singh A, Singh N, Behera D, Sharma S. Genetic polymorphisms in GSTM1, GSTT1 and GSTP1 genes and risk of lung cancer in a North Indian population. *Cancer Epidemiol* 2015;39:947–55.
174. Girdhar Y, Singh N, Behera D, Sharma S. Combinations of the variant genotypes of CYP1A1, GSTM1 and GSTT1 are associated with an increased lung cancer risk in north indian population: a case-control study. *Pathol Oncol Res* 2016;22:647–52.
175. Singh A, Singh N, Behera D, Sharma S. Association and multiple interaction analysis among five XRCC1 polymorphic variants in modulating lung cancer risk in North Indian population. *DNA Repair* 2016;47:30–41.
176. Kumari A, Bahl C, Singh N, Behera D, Sharma S. Association of p53 codon 72 polymorphism and survival of North Indian lung cancer patients treated with platinum-based chemotherapy. *Mol Biol Rep* 2016;43:1383–94.
177. Girdhar Y, Singh N, Behera D, Sharma S. Synergistic association of CYP1A1 polymorphisms with increased susceptibility to squamous cell lung cancer in north Indian smokers. *Int J Biol Markers* 2016;31:e402–e412.
178. Watts A, Singh B, Basher R, Singh H, Bal A, Kapoor R, *et al*. 68Ga-Pentixafor PET/CT demonstrating higher CXCR4 density in small cell lung carcinoma than in non-small cell variant. *Eur J Nucl Med Mol Imag* 2017;44:909–10.
179. Bahl C, Singh N, Behera D, Sharma S. Association of polymorphisms in Dickopff (DKK) gene towards modulating risk for lung cancer in north Indians. *Future Oncol* 2017;13:213–32.
180. Lawania S, Singh N, Behera D, Sharma S. XPC polymorphism and risk for lung cancer in north indian patients treated with platinum based chemotherapy and its association with clinical outcomes. *Pathol Oncol Res* 2018;24:353–66.
181. Bahl C, Sharma S, Singh N, Behera D. Association study between genetic variations in Axin2 gene and lung cancer risk in North Indian population: a multiple interaction analysis. *Tumour Biol* 2017;39:1010428317695533. doi: 10.1177/1010428317695533.
182. Singh A, Singh N, Behera D, Sharma S. Polymorphism in XRCC1 gene modulates survival and clinical outcomes of advanced North Indian lung cancer patients treated with platinum-based doublet chemotherapy. *Med Oncol* 2017;34:64. DOI: 10.1007/s12032-017-0923–4.
183. Lawania S, Singh N, Behera D, Sharma S. Association of XPA polymorphisms towards lung cancer susceptibility and its predictive role in overall survival of North Indians. *Biochem Genet* 2018;56:375–96.
184. Bhardwaj A, Bahl C, Sharma S, Singh N, Behera D. Interactive potential of genetic polymorphism in xenobiotic metabolising and DNA repair genes for predicting lung cancer predisposition and overall survival in North Indians. *Mutat Res* 2018;826:15–24.
185. Singh A, Singh N, Behera D, Sharma S. Role of polymorphic XRCC6 (Ku70)/XRCC7 (DNA-PKcs) genes towards susceptibility and prognosis of lung cancer patients undergoing platinum based doublet chemotherapy. *Mol Biol Rep* 2018;45:253–61.
186. Singh A, Singh N, Behera D, Sharma S. Genetic investigation of polymorphic OGG1 and MUTYH genes towards increased susceptibility in lung adenocarcinoma and its impact on overall survival of lung cancer patients treated with platinum based chemotherapy. *Pathol Oncol Res* 2019;25:1327–40. doi: 10.1007/s12253-017-0372–6.

187. Lawania S, Singh N, Behera D, Sharma S. Xeroderma pigmentosum complementation group D polymorphism toward lung cancer susceptibility survival and response in patients treated with platinum chemotherapy. *Future Oncol* 2017;13:2645–65.

188. Pandey A, Bahl C, Sharma S, Singh N, Behera D. Functional role of cyclinD1 polymorphism (G870A) in modifying susceptibility and overall survival of North Indian lung cancer patients. *Tumori* 2017;104:179–87. doi: 10.5301/tj.5000707.

189. Lawania S, Sharma S, Singh N, Behera D. XPF polymorphism toward lung cancer susceptibility and survival in patients treated with platinum-based chemotherapy. *Future Oncol* 2018;14:1071–89.

190. Bahl C, Singh N, Behera D, Sharma S. High-order gene interactions between the genetic polymorphisms in Wnt and AhR pathway in modulating lung cancer susceptibility. *Per Med* 2017;14:487–502.

191. Budhwar S, Bahl C, Sharma S, Singh N, Behera D. Role of sequence variations in AhR gene towards modulating smoking induced lung cancer susceptibility in North Indian population: a multiple interaction analysis. *Curr Genomics* 2018;19:313–26.

192. Bandyopadhyay A, Sharma S, Behera D, Singh N. UGT1A1 gene polymorphisms in patients with small cell lung cancer treated with irinotecan-platinum doublet chemotherapy and their association with gastrointestinal toxicity and overall survival. On cologist 2021;26:701–13.

193. Bahl C, Singh N, Behera D, Sharma S. Genetic variants in the wingless antagonist genes (sFRP, DKK, and Axin2) predict the overall survival and prognosis of North Indian lung cancer patients treated with platinum-based doublet chemotherapy. *Cancer Biother Radiopharm* 2018;33:466–77.

194. Lawania S, Singh N, Behera D, Sharma S. XPG polymorphisms and their association with lung cancer susceptibility, overall survival and response in North Indian patients treated with platinum-based doublet chemotherapy. *Future Oncol* 2019;15:151–65.

195. Lawania S, Singh A, Sharma S, Singh N, Behera D. The multi-faceted high order polymorphic synergistic interactions among nucleotide excision repair genes increase the risk of lung cancer in North Indians. *Mutat Res* 2019;8:816–8.

196. Singh A, Singh N, Behera D, Sharma S. XRCC1 632 as a candidate for cancer predisposition via a complex interaction with genetic variants of base excision repair and double strand break repair genes. *Future Oncol* 2019;15:3845–59.

197. Engels EA. Inflammation in the development of lung cancer: epidemiological evidence. *Expert Rev Anticancer Ther* 2008;8:605–15.

198. Engels EA, Shen M, Chapman RS, Pfeiffer RM, Yu YY, He *et al*. Tuberculosis and subsequent risk of lung cancer in Xuanwei, China. *Int J Cancer* 2009;124:1183–7.

199. Nalbandian A, Yan BS, Pichugin A, Bronson RT, Kramnik I. Lung carcinogenesis induced by chronic tuberculosis infection: the experimental model and genetic control. *Oncogene* 2009;28:1928–38.

200. Yu YY, Pinsky PF, Caporaso NE, Chatterjee N, Baumgarten M, Langenberg P, *et al*. Lung cancer risk following detection of pulmonary scarring by chest radiography in the prostate, lung, colorectal, and ovarian cancer screening trial. *Arch Intern Med* 2008;168:2326–32.

201. Liang HY, Li XL, Yu XS, Guan P, Yin ZH, He QC, *et al*. Facts and fiction of the relationship between preexisting tuberculosis and lung cancer risk: a systematic review. *Int J Cancer* 2009;125:2936–44.

202. Shiels MS, Albanes D, Virtamo J, Engels EA. Increased risk of lung cancer in men with tuberculosis in the alpha-tocopherol, beta-carotene cancer prevention study. *Cancer Epidemiol Biomarkers Prev* 2011;20:672–8.

203. Dasgupta P, Choudhury K, Paul N, Choudhury KB, Roy B, Maity S. Association of pulmonary tuberculosis with lung carcinoma: an epidemiological study. *Clin Cancer Investig J* 2018;7:199–202.

204. Dacosta NA, Kinare SG. Association of lung carcinoma and tuberculosis. *J Postgrad Med* 1991;37:185–9.

205. Chai M, Shi Q. The effect of anti-cancer and anti-tuberculosis treatments in lung cancer patients with active tuberculosis: a retrospective analysis. *BMC Cancer* 2020; 1121 (2020). https://doi.org/10.1186/s12885-020-07622-6

206. Bhatt M, Kant S, Bhaskar R. Pulmonary tuberculosis as differential diagnosis of lung cancer. *South Asian J Cancer*. 2012;1:36-42. doi:10.4103/2278-330X.96507

207. Gupta RC, Dixit R, Sharma KK, Gupta N. Scar cancer of the lung: current concepts and literature review. *Lung India* 2000;18:84–88.

208. Singh N, Aggarwal AN, Gupta D, Behera D. Prevalence of low body mass index among newly diagnosed lung cancer patients in North India and its association with smoking status. *Thorac Can* 2011;2:27–31.

209. Singh N, Aggarwal AN, Gupta D, Behera D, Jindal SK. Quantified smoking status and non-small cell lung cancer stage at presentation: analysis of a North Indian cohort and a systematic review of literature. *J Thorac Dis* 2012;474–84.

210. Aggarwal AN, Singh N, Gupta D, Behera D. Does awareness of diagnosis influence health related quality of life in north Indian patients with lung cancer? *Indian J Med Res* 2016;143(Suppl.):S38-S44.

211. Yogananda MN, Muthu V, Prasad KT, Kohli A, Behera D, Singh N. Utility of the revised Edmonton Symptom Assessment System (ESAS-r) and the Patient-Reported Functional Status (PRFS) in lung cancer patients. *Support Care Cancer* 2018;26:767–75.

212. Singh N, Singh PS, Aggarwal AN, Behera D. Comorbidity assessment using charlson comorbidity index and simplified comorbidity score and its association with clinical outcomes during first-line chemotherapy for lung cancer. *Clin Lung Cancer* 2016;17:205–13.

213. Singh N, Baldi M, Behera D. Inclusion of lymphangitis as a descriptor in the new TNM staging of lung cancer. *J Thorac Oncol* 2015;10:e119.

214. Singh N, Aggarwal AN, Gupta D, Behera D, Jindal SK. Unchanging clinico-epidemiological profile of lung cancer in north India over three decades. *Cancer Epidemiol* 2010;34:101–4.

215. Yenge LB, Behera D, Garg M, Aggarwal AN, Singh N. Comparison of symptom score and bronchoscopy-based assessment with conventional computed tomography-based assessment of response to chemotherapy in lung cancer. *J Global Oncol* 2017;3:370–9.

216. Singh N, Kulkarni P, Aggarwal AN, Mittal BR, Gupta N, Behera D, *et al*. Choroidal metastasis as a presenting manifestation of lung cancer: a report of 3 cases and systematic review of the literature. *Medicine* (Baltimore) 2012;91:179–94.

217. Purandare NC, Rangarajan V. Imaging of lung cancer: implications on staging and management. *Indian J Radiol Imaging* 2015;25:109–20.

218. Prakashini K, Babu S, Rajgopal KV, Kokila KR. Role of computer aided diagnosis (CAD) in the detection of pulmonary nodules on 64 row multi detector computed tomography. *Lung India* 2016;33:391–7.

219. Garg PK, Singh SK, Prakash G, Jakhetiya A, Pandey D. Role of positron emission tomography-computed tomography in non-small cell lung cancer. *World J Methodol* 2016;6:105–11.

220. Gupta AA, Sehgal IS, Dhooria S, Singh N, Aggarwal AN, Gupta D, *et al.* Indications for performing flexible bronchoscopy: trends over 34 years at a tertiary care hospital. *Lung India* 2015;32:211–5.

221. Dhooria S, Aggarwal AN, Singh N, Gupta D, Behera D, Gupta N, *et al.* Endoscopic ultrasound-guided fine-needle aspiration with an echobronchoscope in undiagnosed mediastinal lymphadenopathy: first experience from India. *Lung India* 2015;32:6–10.

222. Dhooria S, Aggarwal AN, Gupta D, Behera D, Agarwal R. Utility and safety of endoscopic ultrasound with bronchoscope-guided fine-needle aspiration in mediastinal lymph node sampling: systematic review and meta-analysis. *Respir Care* 2015;60:1040–50.

223. Dhooria S, Agarwal R, Aggarwal AN, Gupta N, Gupta D, Behera D. Agreement of mediastinal lymph node size between computed tomography and endobronchial ultrasonography: a study of 617 patients. *Ann Thorac Surg* 2015;99:1894–8.

224. Maturu VN, Dhooria S, Bal A, Singh N, Aggarwal AN, Gupta D, *et al.* Role of medical thoracoscopy and closed-blind pleural biopsy in undiagnosed exudative pleural effusions: a single-center experience of 348 patients. *J Bronchol Interv Pulmonol* 2015;22:121–9.

225. Kaur H, Dhooria S, Aggarwal AN, Gupta D, Behera D, Agarwal R. A randomized trial of 1% vs. 2% lignocaine by the spray-as-you-go technique for topical anesthesia during flexible bronchoscopy. *Chest* 2015;148:739–45. doi: 10.1378/chest.15-0022.

226. Maturu VN, Sehgal IS, Dhooria S, Bal A, Aggarwal AN, Behera D, *et al*. Pleuroscopic cryobiopsy: case series and systematic review. *J Bronchol Interv Pulmonol* 2015;22:e11-3.

227. Mohan A, Madan K, Hadda V, Tiwari P, Mittal S, Guleria R, *et al*. Guidelines for diagnostic flexible bronchoscopy in adults. Joint Indian Chest Society/ National College of Chest Physicians (I)/Indian Association for Bronchology recommendations. *Lung India* 2019;36(Suppl.):S37–S89.

228. Sehgal IS, Dhooria S, Aggarwal AN, Behera D, Agarwal R. Use of radial probe endobronchial ultrasound for the diagnosis of peripheral pulmonary lesion: first report from India. *Lung India* 2016;33:212–5.

229. Dhooria S, Sehgal IS, Bal A, Aggarwal AN, Behera D, Agarwal R. Transbronchial lung biopsy with a flexible cryoprobe during rigid bronchoscopy: standardizing the procedure. *Lung India* 2016;33:248–9.

230. Maturu VN, Dhooria S, Agarwal R, Behera D. Endobronchial ultrasound-guided aspiration of an endotracheal bronchogenic cyst: case report and systematic review of the literature. *J Bronchol Interv Pulmonol* 2016;23:163–7.

231. Dhooria S, Bal A, Sehgal IS, Aggarwal AN, Behera D, Agarwal R. Transbronchial lung biopsy with a flexible cryoprobe: first case report from India. *Lung India* 2016;33:64–68.

232. Sehgal IS, Dhooria S, Gupta N, Bal A, Ram B, Aggarwal AN, *et al.* Impact of endobronchial ultrasound (EBUS) training on the diagnostic yield of conventional transbronchial needle aspiration for lymph node stations 4R and 7. *PLoS One* 2016;11:e0153793. doi: 10.1371/ journal.pone.0153793. eCollection 2016.

233. Dhooria S, Sehgal IS, Gupta N, Ram B, Aggarwal AN, Behera D, *et al.* Yield of new *versus* reused endobronchial ultrasound-guided transbronchial needle aspiration needles: a retrospective analysis of 500 patients. *Lung India* 2016;33:367–71.

234. Sehgal IS, Dhooria S, Aggarwal AN, Behera D, Agarwal R. Endosonography *versus* mediastinoscopy in mediastinal staging of lung cancer: systematic review and meta-analysis. *Ann Thorac Surg* 2016;102:1747–55.

235. Dhooria S, Sehgal IS, Gupta N, Aggarwal AN, Behera D, Agarwal R. Diagnostic yield and complications of EBUS-TBNA performed under bronchoscopist-directed conscious sedation: single center experience of 1004 subjects. *J Bronchol Interv Pulmonol* 2017;24:7–14.

236. Watts A, Singh B, Basher R, Singh H, Bal A, Kapoor R, *et al.* 68Ga-Pentixafor PET/CT demonstrating higher CXCR4 density in small cell lung carcinoma than in non-small cell variant. *Eur J Nucl Med Mol Imaging* 2017;44:909–10.

237. Dhooria S, Sehgal IS, Gupta N, Aggarwal AN, Behera D, Agarwal R. Role of radial endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of pulmonary nodules: case report and literature review. *Lung India* 2017;34:61–64.

238. Vashistha V, Choudhari C, Garg A, Gupta A, Parthasarathy G, Jain D, *et al*. The time required to diagnose and treat lung cancer in Delhi, India: an updated experience of a public referral center. *Appl Cancer Res* 2019;39:11. https://doi.org/10.1186/s41241-019-0080-5.

239. Dhooria S, Sehgal IS, Prasad KT, Bal A, Aggarwal AN, Behera D, *et al.* A randomized trial of antimicrobial prophylaxis in patients undergoing medical thoracoscopy (APT). *Respiration* 2017;94:207–15.
240. Radhakrishnan RK, Mittal BR, Gorla AKR, Basher RK, Sood A, Bal A, *et al.* Real-time intraprocedural 18F-FDG PET/CT-guided biopsy using automated robopsy arm (ARA) in the diagnostic evaluation of thoracic lesions with prior inconclusive biopsy results: initial experience from a tertiary health care centre. *Br J Radiol* 2017;90(1080):20170258. doi: 10.1259/bjr.20170258.
241. Nambirajan A, Longchar M, Madan K, Mallick SR, Kakkar A, Mathur S, *et al.* Endobronchial ultrasound-guided transbronchial needle aspiration cytology in patients with known or suspected extra-pulmonary malignancies: a cytopathology–based study. *Cytopathology* 2019;30:82–90.
242. Thangakunam B, Christopher DJ, James P, Gupta R. Semi-rigid thoracoscopy: initial experience from a tertiary care hospital. *Indian J Chest Dis Allied Sci* 2010;52:25–27.
243. Nattusamy L, Madan K, Mohan A, Hadda V, Jain D, Madan NK, *et al.* Utility of semi-rigid thoracoscopy in undiagnosed exudative pleural effusion. *Lung India* 2015;32:119–26.
244. Mohan A, Naik S, Naseer R, Boon C, Mills J, Pandey RM, *et al*. Performance characteristics of semirigid thoracoscopy in pleural effusions of undetermined etiology. *J Bronchol Interv Pulmonol* 2010;17:289–94.
245. Mohan A, Chandra S, Agarwal D, Naik S, Munavvar M. Utility of semirigid thoracoscopy in the diagnosis of pleural effusions: a systematic review. *J Bronchol Interv Pulmonol* 2010;17:195–201.
246. Mehta A, Rajesh V, Vishwam D, Sethu B, Varun P, Lakshmanan H, *et al*. Value of semirigid thoracoscopy in pleural effusion. *Pulmon* 2010;12:43–5.
247. Prabhu VG, Narasimhan R. The role of pleuroscopy in undiagnosed exudative pleural effusion. *Lung India* 2012;29:128–30.
248. Dhooria S, Singh N, Aggarwal AN, Gupta D, Agarwal R. A randomized trial comparing the diagnostic yield of rigid and semirigid thoracoscopy in undiagnosed pleural effusions. *Respir Care* 2014;59:756–64.
249. Mootha VK, Agarwal R, Singh N, Aggarwal AN, Gupta D, Jindal SK. Medical thoracoscopy for undiagnosed pleural effusions: experience from a tertiary care hospital in north India. *Indian J Chest Dis Allied Sci* 2011;53:21–4.
250. Khan MA, Ambalavanan S, Thomson D, Miles J, Munavvar M. A comparison of the diagnostic yield of rigid and semirigid thoracoscopes. *J Bronchol Interv Pulmonol* 2012;19:98–101.
251. Khandelwal A, Seem R, Gupta M, Rana MK, Prakash H, Vasquez KM, *et al*. Circulating microRNA-590-5p functions as a liquid biopsy marker in non-small cell lung cancer. *Cancer Sci* 2020;111:826–39.
252. Maturu VN, Singh N, Bal A, Gupta N, Das A, Behera D. Relationship of epidermal growth factor receptor activating mutations with histologic subtyping according to International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society 2011 adenocarcinoma classification and their impact on overall survival. *Lung India* 2016;33:257–66.
253. Bal A, Singh N, Agarwal P, Das A, Behera D. ALK gene rearranged lung adenocarcinomas: molecular genetics and morphology in cohort of patients from North India. *Acta Pathol Microbiol Immunol Scandinavica* 2016;124:832–8.
254. Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, *et al.* The effect of advances in lung-cancer treatment on population mortality. *N Engl J Med* 2020;383:640–9.
255. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, *et al* and the CONCORD Working Group. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37,513,025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018;391:1023–75.
256. Hanna NH, Schneider BJ, Temin S, Baker S Jr, Brahmer J, Ellis PM, *et al.* Therapy for stage IV non–small-cell lung cancer without driver alterations: ASCO and OH (CCO) Joint Guideline Update. *J Clin Oncol* 2020 38:1608–32.
257. Hanna NH, Robinson AG, Temin S, Baker S Jr, BrahmerJ R, Ellis PM, *et al*. Therapy for stage IV non–small-cell lung cancer with driver alterations: ASCO and OH (CCO) Joint Guideline Update. *J Clin Oncol* 2021;39:1040–91.
258. Shajeem O, Behera D, Aggarwal AN. Chemotherapy *versus* best supportive care in the management of lung cancer. *J Assoc Physicians India* 2003;51:261–4.
259. Behera D. Managing lung cancer in developing countries: difficulties and solutions. *Indian J Chest Dis Allied Sci* 2006;48:243–4.
260. Behera D. New approach to the treatment of lung cancer: the molecular targeted therapy. *Indian J Chest Dis Allied Sci* 2007;49:149–58.
261. Behera D. Aggarwal R. Aggarwal AN, Gupta D, Jindal SK, Sharma SC, *et al*. A cheap and affordable combination chemotherapy (irinotecan and cisplatin) for treatment of lung cancer in developing countries: observations from India. *J Thorac Oncol* 2007;2(Suppl. 4):S667.
262. Behera D, Aggarwal R, Aggarwal AN, Gupta D, Jindal SK, Sharma SC, *et al.* Gefitinib (Gefitinat) in advanced non small cell lung cancer:a follow up observation in Indian patients. *J Thorac Oncol* 2007;2(Suppl. 4):S705.
263. Singh N, Potsangbam SS, Aggarwal AN, Behera D. 442PGraded baseline symptom (BS) assessment in lung cancer (LC) patients (pts) undergoing first line chemotherapy (CTx)–correlations and prognostic role. *Ann Oncol* 2016;26(Suppl. 9): ix134–ix134.
264. Parikh P, Bhattacharyya GS, Chaturvedi P, Chaudhry K, Rath GK, Behera D, *et al.* Prevention In lung cancer: a vision from India. *Ann Oncol* 2008;19:37.
265. Singh N, Aggarwal AN, Behera D, Jindal SK. Inter-cycle delays during chemotherapy of non-small cell lung cancer

in a health-care resource constrained setting and their effect on overall survival. *J Thorac Oncol* 2010;5:236–9.

266. Singh N, Bal A, Aggarwal AN, Das A, Behera D. Clinical outcomes in non-small cell lung cancer in relation to expression of predictive and prognostic biomarkers. *Future Oncol* 2010;6:741–67.
267. Behera D, Jaiswal A, Saini J, Nagar D, Jaiswal A, Saini J, *et al*. Cisplatin and irinotecan combination chemotherapy in non-small cell lung cancer patients attending a TB hospital in India. *J Thoracic Oncol* 2011;6:S1209–S1210.
268. Blumenschein GR Jr, Kabbinavar F, Menon H, Mok TS, Stephenson J, Beck JT, *et al*. A phase II, multicenter, open-label randomized study of motesanib or bevacizumab in combination with paclitaxel and carboplatin for advanced nonsquamous non-small-cell lung cancer. *Ann Oncol* 2011;22:2057–67.
269. Singh N, Aggarwal AN, Behera D. Management of advanced lung cancer in resource-constrained settings: a perspective from India. *Expert Rev Anticancer Ther* 2012;12:1479–95.
270. Murali AN, Radhakrishnan V, Ganesan TS, Rajendranath R, Ganesan P, Selvaluxmy G, *et al*. Outcomes in lung cancer: 9-year experience from a tertiary cancer center in India. *J Glob Oncol* 2017;3:459–68.
271. Singh N, Mootha VK, Madan K, Aggarwal AN, Behera D. Tumor cavitation among lung cancer patients receiving first-line chemotherapy at a tertiary care centre in India: association with histology and overall survival. *Med Oncol* 2013;30:602. DOI: 10.1007/s12032-013-0602-z.
272. Mallick I, Sharma SC, Behera D. Endobronchial brachy-therapy for symptom palliation in non-small cell lung cancer: analysis of symptom response, endoscopic improvement and quality of life. *Lung Cancer* 2007;55:313–8.
273. Behera D, Aggarwal R, Agarwal AN, Gupta D, Jindal SK, Sharma SC, *et al.* Cost effective chemotherapy (irinoteca and cisplatin) for treatment of lung cancer in developing countries: observations from India. *J Clin Oncol* 2008;26:(Suppl. 15) 19121. DOI: 10.1200/jco.2008.26.15_suppl.19121.
274. Maturu VN, Singh N, Bansal P, Rai Mittal B, Gupta N, Behera D, *et al.* Combination of intravitreal bevacizumab and systemic therapy for choroidal metastases from lung cancer: report of two cases and a systematic review of literature. *Med Oncol* 2014;31:901doi: 10.1007/s12032-014-0901-z
275. Singh N, Aggarwal AN, Kaur J, Behera D. Association of graded folic acid supplementation and total plasma homocysteine levels with hematological toxicity during first-line treatment of non-squamous NSCLC patients with pemetrexed based chemotherapy. *Am J Clin Oncol* 2017;40:75-82. doi: 10.1097/COC.0000000000000111.
276. Singh N, Vishwanath G, Aggarwal AN, Behera D. Clinical experience on use of oral EGFR TKIs as first line treatment of advanced NSCLC from a tertiary care centre in North India and implications of skin rash. *Indian J Chest Dis Allied Sci* 2014;56:149–52.
277. Roy S, Pathy S, Kumar R, Mohanti BK, Raina V, Jaiswal A, *et al*. Efficacy of PET-CT in evaluation of response in locally advanced non-small cell lung cancer. *Ann Oncol* 2014:25 (Suppl. 4):iv 24-iv424.
278. Singh N, Jindal A, Behera D. Erlotinib usage after prior treatment with gefitinib in advanced non-small cell lung cancer: a clinical perspective and review of published literature. *World J Clin Oncol* 2014;5:858–64.
279. Behera D, Singh N, Maturu VN, Sehgal IS. Clinical experience with oral topotecan in relapsed small cell lung cancer patients following irinotecan-platinum chemotherapy. *J Postgrad Med Edu Res* 2016;50:110–11.
280. Singh N, Maturu VN, Behera D. Total plasma homocysteine level assessment and timing of folate/B12 supplementation prior to initiation of pemetrexed-based chemotherapy for nonsquamous non-small cell lung cancer patients: an irrelevant investigation, an unnecessary delay, or both? *Oncologist* 2015;20:e21.
281. Kumar S, Saikia J, Kumar V Jr, Malik PS, Madan K, Jain D, *et al*. Neoadjuvant chemotherapy followed by surgery in lung cancer: Indian scenario. *Curr Probl Cancer* 2020;44:100563.doi:10.1016/j.currproblcancer.2020.100563.
282. Behera D, Pillai AKK. Screening for EGFR gene mutations, their clinicopathologic correlates and patient outcomes: a single centre experience from north India. *Indian J Pub Health* 2016;60:81.
283. Mohapatra PR. Optimizing the management of lung cancer: role of the pulmonologist in India. *Lung India* 2013;30:173-4.
284. Singh PS, Aggarwal AN, Behera D, Kapoor R, Singh N. Simplified graded baseline symptom assessment in patients with lung cancer undergoing first-line chemotherapy: correlations and prognostic role in a resource-constrained setting. *J Glob Oncol* 2016;3:54–63.
285. Singh N, Maturu VN, Sehgal IS, Kapoor R, Behera D. Clinical experience oral topotecan in replased small cell lung cancer. *J Postgrad Med Edu Res* 2016;50:110–11.
286. Baldi M, Behera D, Kaur J, Kapoor R, Singh N. Rationale and design of PEMVITASTART: an open-label randomized trial comparing simultaneous *versus* standard initiation of vitamin B12 and folate supplementation in nonsquamous, non-small-cell lung cancer patients undergoing first-line pemetrexed-based chemotherapy. *Clin Lung Cancer* 2017;18:432–5.
287. Singh A, Singh N, Behera D, Sharma S. Polymorphism in XRCC1 gene modulates survival and clinical outcomes of advanced North Indian lung cancer patients treated with platinum-based doublet chemotherapy. *Med Oncol* 2017;34:64. doi: 10.1007/s12032-017-0923-4. Epub 2017 Mar 22.
288. Yenge LB, Behera D, Garg M, Aggarwal AN, Singh N. Comparison of symptom score and bronchoscopy-based assessment with conventional computed tomography-based assessment of response to chemotherapy in lung cancer. *J Glob Oncol* 2016;3:370–9.
289. Muthu V, Mylliemngap B, Prasad KT, Behera D, Singh N. Adverse effects observed in lung cancer patients undergoing first-line chemotherapy and effectiveness of supportive care drugs in a resource-limited setting. *Lung India* 2019;36:32–37.

290. Singh N, Baldi M, Kaur J, Muthu V, Prasad KT, Behera D, *et al*. Timing of folic acid/vitamin B12 supplementation and hematologic toxicity during first-line treatment of patients with nonsquamous non-small cell lung cancer using pemetrexed-based chemotherapy: The PEMVITASTART randomized trial. *Cancer* 2019;125:2203–12. doi: 10.1002/cncr.32028.

291. Soni A, Rastogi A, Prasad KT, Behera D, Singh N. Thyroid dysfunction in non-small cell lung cancer patients treated with epidermal growth factor receptor and anaplastic lymphoma kinase inhibitors: results of a prospective cohort. *Lung Cancer* 2021;151:16–19.

292. Singh N, Agrawal S, Jiwnani S, Khosla D. Malik PS, Mohan A, *et al*. Lung cancer in India. *J Thorac Oncol* 2021;16:1250–66.

293. Deepa KV, Venghateri JB, Khajanchi M, Gadgil A, Roy N. Cancer epidemiology literature from India: does it reflect the reality? *J Public Health* 2020;42:e421–e427.

294. Behera D, Aggarwal AN, Sharma SC, Gupta D, Jindal SK. Ifosfamide containing regimen for non-small cell lung cancer. *Indian J Chest Dis Allied Sci* 2004;46:9–15.

295. Natukula K, Jamil K, Pingali UR, Suresh Attili VS, Naidu Madireddy UR. Survival analysis in advanced non small cell lung cancer treated with platinum based chemotherapy in combination with paclitaxel, gemcitabine and etoposide. *Asian Pac J Cancer Prev* 2013;14:4661–6.

296. Rajappa S, Gundeti S, Talluri MR, Digumarti R. Chemotherapy for advanced lung cancer: a 5–year experience. *Indian J Cancer* 2008;45:20–26.

297. Pathak AK, Bhutani M, Guleria R, Bal S, Mohan A, Mohanti BK, *et al.* Chemotherapy alone vs chemotherapy plus high dose multiple antioxidants in patients with advanced non small cell lung cancer. *J Am Coll Nutr* 2005;24:16–21.

298. Bala S, Gundeti S, Linga VG, Maddali LS, Digumarti RR, Uppin SG, *et al*. Clinicopathological features and outcomes in advanced nonsmall cell lung cancer with tailored therapy. *Indian J Med Paediatr Oncol* 2016;37:242–50.

299. Hingmire SS, Sambhus MB, Kelkar DS, Joshi SW, Narsinghpura KS. First–line therapy outcomes in patients with advanced stage nonsmall cell lung cancer treated at nongovernment tertiary care centrer in India: experience from a real world practice. *Indian J Cancer* 2017;54:182–6.

300. Doval DC, Sinha R, Batra U, Choudhury KD, Azam S, Mehta A, *et al.* Clinical profile of nonsmall cell lung carcinoma patients treated in a single unit at a tertiary cancer care center. *Indian J Cancer* 2017;54:193–6.

301. Babu KG, Prabhash K, Vaid AK, Sirohi B, Diwakar RB, Rao R, *et al.* Nimotuzumab plus chemotherapy *versus* chemotherapy alone in advanced non-small-cell lung cancer: a multicenter, randomized, open-label phase II study. *Onco Targets Ther* 2014;7:1051–60.

302. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, *et al.* Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543–51.

303. Louis RA, Rajendranath R, Ganesan P, Sagar TG, Krishnamurthy A. First report of upfront treatment with gefitinib in comparison with chemotherapy in advanced non-small cell lung cancer patients from South India: analysis of 120 patients. *Indian J Med Paediatr Oncol* 2012;33:146–54.

304. Paliwal P, Rajappa S, Santa A, Mohan M, Murthy S, Lavanya N, *et al*. Clinical profile and outcomes of patients with stage IV adenocarcinoma of lung: a tertiary cancer center experience. *Indian J Cancer* 2017;54:197–202.

305. Yang JC, Kang JH, Mok T, Ahn MJ, Srimuninnimit V, Lin CC, *et al.* First-line pemetrexed plus cisplatin followed by gefitinib maintenance therapy *versus* gefitinib monotherapy in East Asian patients with locally advanced or metastatic non-squamous non-small cell lung cancer: a randomised, phase 3 trial. *Eur J Cancer* 2014;50:2219–30.

306. Yang JC, Srimuninnimit V, Ahn MJ, Lin CC, Kim SW, Tsai CM, *et al.* First-line pemetrexed plus cisplatin followed by gefitinib maintenance therapy *versus* gefitinib monotherapy in East Asian never-smoker patients with locally advanced or metastatic nonsquamous non-small cell lung cancer: final overall survival results from a randomized phase 3 study. *J Thorac Oncol* 2016;11:370–9.

307. Patil VM, Noronha V, Joshi A, Choughule AB, Bhattacharjee A, Kumar R, *et al*. Phase III study of gefitinib or pemetrexed with carboplatin in EGFR-mutated advanced lung adenocarcinoma. *ESMO Open* 2017;2:e000168.

308. Gridelli C, de Marinis F, Thomas M, Prabhash K, El Kouri C, Blackhall F, *et al*. Final efficacy and safety results of pemetrexed continuation maintenance therapy in the elderly from the PARAMOUNT phase III study. *J Thorac Oncol* 2014;9:991–7.

309. Pandey AV, Phillip DS, Noronha V, Joshi A, Janu A, Jambekar N, *et al*. Maintenance pemetrexed in nonsmall cell lung carcinoma: outcome analysis from a tertiary care center. *Indian J Med Paediatr Oncol* 2015;36:238–42.

310. Pandey A, Noronha V, Joshi A, Prabhash K. Switch maintenance tyrosine kinase inhibitors in EGFR mutation positive metastatic non-squamous NSCLC: experience from the real world. *Gulf J Oncol* 2016;1:6–10.

311. Pankaj G, Ullas B, Doval DC, Parveen J, Amitabh UK, Dash PK, *et al.* Efficacy and toxicity profile of maintenance pemetrexed in patients with stage IV adenocarcinoma lung in Indian population. *South Asian J Cancer* 2016;5:196–203.

312. Murali AN, Radhakrishnan V, Ganesan TS, Rajendranath R, Ganesan P, Selvaluxmy G, *et al*. Outcomes in lung cancer: 9-year experience from a tertiary cancer center in India. *J Glob Oncol* 2017;3:459–68.

313. Mohan A, Poulose R, Gupta T, Luthra K, Pandey RM, Madan K, *et al.* Impact of chemotherapy on symptom profile, oxidant-antioxidant balance and nutritional status in non-small cell lung cancer. *Lung India* 2017;34:336–40.

314. Veldore VH, Rao RM, Kakara S, Pattanayak S, Tejaswi R, Sahoo R, *et al*. Epidermal growth factor receptor mutation in non-small-cell lung carcinomas: a retrospective analysis of 1036 lung cancer specimens from a network of tertiary cancer care centers in India. *Indian J Cancer* 2013;50:87–93.
315. Mehta J. Molecular epidemiology of epidermal growth factor receptor mutations in lung cancers in Indian population. *Indian J Cancer* 2013;50:102–6.
316. Parikh P, Chang AY, Nag S, Digumarti R, Bhattacharyya GS, Doval DC, *et al.* Clinical experience with gefitinib in Indian patients. *J Thorac Oncol* 2008;3:380–5.
317. Louis RA, Rajendranath R, Ganesan P, Sagar TG, Krishnamurthy A. First report of upfront treatment with gefitinib in comparison with chemotherapy in advanced non-small cell lung cancer patients from South India: analysis of 120 patients. *Indian J Med Paediatr Oncol* 2012;33:146–54.
318. Bhatt AD, Pai R, Rebekah G, Nehru GA, Dhananjayan S, Samuel A, *et al*. Clinicopathologic features of non-small cell lung cancer in India and correlation with epidermal growth factor receptor mutational status. *Indian J Cancer* 2013;50:94–101.
319. Noronha V, Prabhash K, Thavamani A, Chougule A, Purandare N, Joshi A, *et al*. EGFR mutations in Indian lung cancer patients: clinical correlation and outcome to EGFR targeted therapy. *PLoS One* 2013;8:e61561.
320. Kaur H, Sehgal IS, Singh N. Chemotherapy regimens for metastatic nonsmall cell lung cancer: generating good quality data is important before challenging evidence. *Lung India* 2016;33:470–2.
321. Kamath MP, Lakshmaiah KC, Babu KG, Loknatha D, Jacob LA, Babu SMC. Pharmacoeconomic benefit of cisplatin and etoposide chemoregimen for metastatic non small cell lung cancer: an Indian study. *Lung India* 2016;33:154–8.
322. Noronha V, Patil VM, Joshi A, Tandon N, Sharma V, Ramaswamy A, *et al.* Epidermal growth factor receptor positive lung cancer: the nontribal scenario. *Indian J Cancer* 2017;54:132–5.
323. Malik PS, Jain D, Kumar L. Epidermal growth factor receptor tyrosine kinase inhibitors in advanced non-small cell lung cancer. *Oncology* 2016;91 (Suppl. 1):26–34.
324. Joshi A, Patil V, Noronha V, Chougule A, Bhattacharjee A, Kumar R, *et al*. Efficacy of gefitinib in epidermal growth factor receptor-activating mutation-positive nonsmall cell lung cancer: does exon 19 deletion differ from exon 21 mutation? *Lung India* 2018;35:27–30.
325. Noronha V, Patil V, Joshi A, Chougule A, Bhattacharjee A, Kumar R, *et al*. Impact of exon 19 *versus* exon 21 EGFR-activating mutation on outcomes with upfront pemetrexed-carboplatin chemotherapy. *E Cancer Med Sci* 2017;11:776.
326. Noronha V, Choughule A, Patil VM, Joshi A, Kumar R, Susan Joy Philip D, *et al.* Epidermal growth factor receptor exon 20 mutation in lung cancer: types, incidence, clinical features and impact on treatment. *Onco Targets Ther* 2017;10:2903–8.
327. Muthu V, Mylliemngap B, Prasad KT, Behera D, Singh N. Adverse effects observed in lung cancer patients undergoing first-line chemotherapy and effectiveness of supportive care drugs in a resource-limited setting. *Lung India* 2019;36:32–37.
328. Under the aegis of Lung Cancer Consortium Asia (LCCA), Indian Cooperative Oncology Network (ICON), Indian Society of Medical and Pediatric Oncology (ISMPO), Molecular Oncology Society (MOS) and Association of Physicians of India API). Indian Consensus Statement for Treatment of Advanced Non-small Cell Lung Cancer: First line, Maintenance, and Second line. *Indian J Cancer* 2017;54:89–103.
329. Noronha V, Chandrakanth MV, Joshi AP, Patil V, Chougule A, Mahajan A, *et al.* ROS1 rearranged non-small cell lung cancer and crizotinib: an Indian experience. *Indian J Cancer* 2017;54:436–8.
330. Dubey AP, Pathi N, Viswanath S, Rathore A, Pathak A, Sud R, *et al*. New insights into anaplastic lymphoma kinase-positive nonsmall cell lung cancer. *Indian J Cancer* 2017;54:203–8.
331. Noronha V, Ramaswamy A, Patil VM, Joshi A, Chougule A, Kane S, *et al.* ALK positive lung cancer: clinical profile, practice and outcomes in a developing country. *PLoS One* 2016;11:e0160752.
332. Joshi AP, Chandrakanth MV, Noronha V, Patil V, Chougule A, Mahajan A, *et al.* Ceritinib in anaplastic lymphoma kinase–positive nonsmall cell lung cancer among patients who were previously exposed to crizotinib: experience from the Indian subcontinent. *Indian J Cancer* 2017;54:144–7.
333. Murthy SS, Rajappa SJ, Gundimeda SD, Mallavarapu KM, Ayyagari S, Yalavarthi P, *et al.* Anaplastic lymphoma kinase status in lung cancers: an immunohistochemistry and fluorescence in situ hybridization study from a tertiary cancer center in India. *Indian J Cancer* 2017;54:231–5.
334. Batra U, Aggarwal M, Jain P, Goyal P, Yadav A, Maheshwari U, *et al.* Clinical outcome study of crizotinib in immunohistochemistry-proven echinoderm microtubule–associated protein-like 4-anaplastic lymphoma kinase fusion gene among Indian patients with adenocarcinoma lung. *South Asian J Cancer* 2018;7:61–64.
335. Bamania A, Sahni D, Mohan A, Malik P, Madan K, Hadda V. Clinical response to crizotinib as a 1st and 2nd line therapy in ALK positive lung cancer in an Indian population. *Am J Respir Crit Care Med* 2017;195:(A4589).
336. Murthy SS, Rajappa SJ, Gundimeda SD, Mallavarapu KM, Ayyagari S, Yalavarthi P, *et al*. Anaplastic lymphoma kinase status in lung cancers: an immunohistochemistry and fluorescence in situ hybridization study from a tertiary cancer center in India. *Indian J Cancer* 2017;54:231–5.
337. Gupta P, Gowrishankar S, Swain M. Epidermal growth factor receptor and anaplastic lymphoma kinase mutation in adenocarcinoma lung: their incidence and correlation with histologic patterns. *Indian J Pathol Microbiol* 2019;62:24–30.

338. Sharma P, Mehta M, Dhanjal DS, Kaur S, Gupta G, Singh H, *et al*. Emerging trends in the novel drug delivery approaches for the treatment of lung cancer. *Chem Biol Interact* 2019;309:108720. doi: 10.1016/j.cbi.2019.06.033.

339. Baldi M, Behera D, Kaur J, Kapoor R, Singh N. Rationale and design of PEMVITASTART: an open-label randomized trial comparing simultaneous *versus* standard initiation of vitamin B_{12} and folate supplementation in nonsquamous, non-small-cell lung cancer patients undergoing first-line pemetrexed-based chemotherapy. *Clin Lung Cancer* 2016. pii: S1525-7304(16)30371-0. doi: 10.1016/j.cllc.2016;11.017.

340. Mehta A, Saifi M, Batra U, Suryavanshi M, Gupta K. Incidence of ROS1-rearranged non-small-cell lung carcinoma in india and efficacy of crizotinib in lung adenocarcinoma patients. *Lung Cancer* (Auckl) 2020;11:19–25.

341. Prasad KT, Muthu V, Biswas B, Malik PS, Dabkara D, Ganguly S, *et al.* Utility and safety of maintenance chemotherapy in advanced non-small cell lung cancer across various performance status categories: real-world experience. *Curr Probl Cancer* 2020;44:100565. doi: 10.1016/j.currproblcancer.2020.100565.

342. Gupta P, Saha K, Vinarkar S, Banerjee S, Choudhury SS, Parihar M, *et al*. Next generation sequencing in lung cancer: an initial experience from India. *Curr Probl Cancer* 2020;44:100562. doi: 10.1016/j.currproblcancer.2020.100562.

343. Garg A, Batra U, Choudhary P, Jain D, Khurana S, Malik PS, *et al.* Clinical predictors of response to EGFR-tyrosine kinase inhibitors in EGFR-mutated non-small cell lung cancer: A real-world multicentric cohort analysis from India. *Curr Probl Cancer* 2020;44:100570. doi: 10.1016/j.currproblcancer.2020.100570.

344. Patel A, Batra U, Prasad KT, Dabkara D, Ghosh J, Sharma M, *et al.* Real world experience of treatment and outcome in ALK-rearranged metastatic nonsmall cell lung cancer: a multicenter study from India. *Curr Probl Cancer* 2020;44:100571. doi: 10.1016/j.currproblcancer.2020.100571.

345. Bandyopadhyay A, Sharma S, Behera D, Singh N. UGT1A1 Gene polymorphisms in patients with small cell lung cancer treated with irinotecan-platinum doublet chemotherapy and their association with gastrointestinal toxicity and overall survival. *Oncologist* 2021 Mar 16. doi: 10.1002/onco.13757.

346. Ghadyalpatil NS, Pandey A, Krishnamani I, Srinivas C, Rafiq SJ, Hingmire SS, *et al.* First-line management of metastatic non-small cell lung cancer: an Indian perspective. *South Asian J Cancer* 2019;8:73–9.

347. Pradhan MR, Patel SK, Prusty RK. Pattern and predictors of tobacco use in India: evidence from National Family Health Survey (2015–2016). *J Health Manage* 2019;21:510–24.

348. Tata Institute of Social Sciences (TISS), Mumbai and Ministry of Health and Family Welfare, Government of India. *Global Adult Tobacco Survey GATS 2 India* 2016-17.

349. Ministry of Health and Family Welfare, World Health Organization, Tata Institute of Social Sciences. *Global Adult Tobacco Survey* (*GATS2*), second round, India, 2016-17. p. 1-360.

350. Youth tobacco use prevalence and exposure to secondhand smoke: Global Youth Tobacco Survey (GYTS) 2009 *Available from URL:* (http://www.searo.who.int/entity/noncommunicable_diseases/data/india_ncd_reports. Accessed on October 10, 2020

351. Singh PK, Yadav A, Singh L, Singh S, Mehrotra R. Social determinants of dual tobacco use in India: an analysis based on the two rounds of global adult tobacco survey. *Prev Med Rep* 2020;18:101073. doi:10.1016/j.pmedr.2020.101073.

352. Mishra GA, Pimple SA, Shastri SS. An overview of the tobacco problem in India. *Indian J Med Paediatr Oncol* 2012;33:139–45.

353. Data on total and proportional deaths from CVDs, tobacco use and proportion of total tobacco deaths due to CVDs: Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD 2016) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME): 2017. *Available from URL:* (http://ghdx.healthdata.org/gbd-results-tool. Accessed on October 10, 2020

354. Jha P, Jacob B, Gajalakshmi V, Gupta PC, Dhingra N, Kumar R, *et al*. A nationally representative case–control study of smoking and death in India. *N Engl J Med* 2008;358:1137–47.

355. Kumar R, Prakash S, Khushwah AS, Kumar H. Smoking cessation-control measures. *Lung India* 2005;22:68–73.

356. Kumar R, Kant S, Chandra A, Krishnan A. Tobacco use and nicotine dependence among newly diagnosed pulmonary tuberculosis patients in Ballabgarh Tuberculosis Unit, Haryana. *J Family Med Prim Care* 2020;9:2860–5.

357. Kumar R, Salve H, Misra F. Determinants of tobacco use and perception, attitude about an antitobacco act in rural Haryana, North India. *Int J Med Public Health* 2014;4:367–70.

358. Vinothkumar G, Girija G, Manikandan M, Vincent A, Newtonraj A. Prevalence and determinants of tobacco use in a remote rural area of South India: a community based cross sectional study. *Int J Community Med Public Health* 2020;7:3499–503.

359. Ministry of Law and Justice. Cigarettes and Other Tobacco Product Act (COTPA). 2002. *Available from URL:* https://www.tobaccocontrollaws.org/files/live/India/India%20-%20COTPA%20-%20national.pdf. Accessed on June 1, 2020.

360. Ministry of Health and Family Welfare. National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS). New Delhi; 2017. *Available from URL:* https://main.mohfw.gov.in/Major-Programmes/non-communicable-diseases-injury-trauma/Non-Communicable-Disease-II/National-Programme-for-Prevention-and-Control-of-Cancer-Diabetes-Cardiovascular-diseases-and-Stroke-NPCDCS. Accessed on October 10, 2020

361. Sharan RN, Chanu TM, Chakrabarty TK, Farsalinos K. Patterns of tobacco and e-cigarette use status in India: a cross-sectional survey of 3000 vapers in eight Indian cities. *Harm Reduct J* 2020;17:21. doi:10.1186/s12954-020-00362-7.
362. Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143 (Suppl. 5):e78S-e92S. doi:10.1378/chest.12-2350.
363. National Cancer Institute. Physician Data Query (PDQ). Patient Version. Lung Cancer Screening. 2019. *Available from URL:* at https://www.cancer.gov/types/lung/patient/lung-screening-pdq. Accessed on May 22, 2019.
364. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, *et al.* Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
365. Pinsky PF, Church TR, Izmirlian G, Kramer BS. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. *Cancer* 2013;119:3976–83.
366. Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, *et al*. Cancer screening in the United States, 2018: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin* 2018;68:297–316.
367. Wender R, Fontham ET, Barrera E Jr, Colditz GA, Church TR, Ettinger DS, *et al.* American Cancer Society lung cancer screening guidelines. *CA Cancer J Clin* 2013;63:107–17.
368. Jin J. Screening for lung cancer. *JAMA* 2021;325:1016. doi:10.1001/jama.2021.1799.
369. Shankar A, Saini D, Dubey A, Roy S, Bharati SJ, Singh N, *et al*. Feasibility of lung cancer screening in developing countries: challenges, opportunities and way forward. *Transl Lung Cancer Res* 2019;8 (Suppl. 1):S106–S121.
370. Vaghasiya K, Sharma A, Verma R. Misdiagnosis murder: disguised TB or lung cancer? *Pul Res Respir Med* 2016;3:e5–6.
371. Singh VK, Chandra S, Kumar S, Pangtey G, Mohan A, Guleria R. A Common medical error: lung cancer misdiagnosed as sputum negative tuberculosis. *Asian Pac J Cancer Prev* 2009;10:335–8.
372. Bhatt M, Kant S, Bhaskar R. Pulmonary tuberculosis as differential diagnosis of lung cancer. *South Asian J Cancer* 2012;1:36.
373. Kashyap S, Anjali S. Lung cancer screening in India: a long way to go. *Indian J Chest Dis All Sci* 2014;54:145–6.
374. Sankaranarayanan R. Screening for cancer in low- and middle-income countries. *Ann Glob Health* 2014;80:412–7.
375. Khanna VK, Ghosh S, MacMohan H, Mehta AC. Criteria for low-dose CT lung cancer screening in the setting of air pollution. *Chest* 2021;159:42–45.
376. Prasad KT, Basher R, Garg M, Grover S, Kalra N, Singh N, *et al.* Utility of LDCT in lung cancer screening in a TB endemic region. Postgraduate Institute of Medical Education and Research, Chandigarh. ClinicalTrials.gov identifier (NCT number): NCT03909620. *Available at URL:* https://clinicaltrials.gov/ct2/show/NCT03909620. Accessed on September 3, 2021.
377. Addeo A, Obeid M, Friedlaender A. COVID-19 and lung cancer: risks, mechanisms and treatment interactions. *J Immuno Ther Cancer* 2020;0:e000892. doi:10.1136/jitc-2020-000892.
378. Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 Transmission in patients with cancer at a tertiary care hospital in Wuhan, China. *JAMA Oncol* 2020;6:1108–10.
379. Mei H, Dong X, Wang Y, Tang L , Hu Y. Managing patients with cancer during the COVID-19 pandemic: frontline experience from Wuhan. *Lancet Oncol* 2020;21:634–6.
380. Yang K, Sheng Y, Huang C, Jin Y, Xiong N, Jiang K, *et al.* Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective cohort study. *Lancet Oncol* 2020; 21:904–13.
381. Tian J, Yuan X, Xiao J, Zhong Q, Yang C, Liu B, *et al.* Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective cohort study. *Lancet Oncol* 2020;21:893–903.
382. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, *et al*. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020;21:335–7.
383. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, *et al*. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol* 2020;31:894–901.
384. Wang H, Zhang L. Risk of COVID-19 for patients with cancer. *Lancet Oncol* 2020;21:e181.
385. Dinmohamed AG, Visser O, Verhoeven RHA, Louwman MWJ, Van Nederveen FH, Willems SM, *et al.* Fewer cancer diagnoses during the COVID-19 epidemic in the Netherlands. *Lancet Oncol* 2020;21:750–51.
386. Kutikov A, Weinberg DS, Edelman MJ, Horwitz EM, Uzzo RG, Fisher RI. A war on two fronts: cancer care in the time of COVID-19. *Ann Intern Med* 2020;2:172:756–8.
387. Calabrò L, Peters S, Soria J, Giacomo AMD, Barlesi F, Covre A, *et al*. Challenges in lung cancer therapy during the COVID-19 pandemic. 2020;8:542–4.
388. The Tata Memorial Centre COVID-19 Working Group. The COVID-19 pandemic and the Tata Memorial Centre response. *Indian J Cancer* 2020;57:123–8.
389. Singh AP, Berman AT, Marmarelis ME, Haas AR, Feigenberg SJ, Braun J, *et al.* Management of lung cancer during the COVID-19 pandemic. *JCO Oncol Pract* 2020;16:579–86.
390. Singh N. Management of lung cancer during the COVID-19 pandemic; practical solutions for resource-constrained settings from adaptions of an international consensus. *Lung India* 2020;37:381–3.

Cont...

ABBRIVATIONS USED IN THIS ARTICLE

ECIS=European Cancer Information System

ICMR=Indian Council of Medical Research

HBCRs=Hospital-based Cancer Registries

NCRP=National Cancer Registry Programme

AARs=Age adjusted ratios

UI=Uncertainty interval

NSCLC-NOS=NSCLC-not otherwise specified

ETD= Extra-thoracic disease

BMI=Body mass index

CR= Crude rate

CUM= Cumulative risk

M/I=….

IHC= Immunohistochemistry

OR=Odds ratio

CI=Confidence interval

ETS= Environmental tobacco smoke

vs=versus

PM= Particulate matter

EGFR= Epidermal growth factor receptor

TB=Tuberculosis

HR= Hazard ratio

IQR= Interquartile range

QTSE= Quantified tobacco smoke exposure

ECOG= Eastern Cooperative Oncology Group

EBUS= Endobronchial ultrasound

PET= Positron emission tomography

CT=Computed tomography

TBLB= Transbronchial lung biopsy

NFHS= National Family and Health Survey

GATS=Global Adult Tobacco Survey

NTCP= National Tobacco Control Programme

COTPA= Cigarettes and Other Tobacco Product Act

LDCT= Low-dose computed tomography

COPD= Chronic obstructive pulmonary disease

NLST= National Lung Cancer Screening Trial