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Patient Characteristics of Secondary Metastatic Bone Disease Due to Primary Lung Cancer in Prof. Dr. IGNG Ngoerah Hospital During 2016-2021: A Descriptive Study

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ABSTRACT

Introduction: The purpose of this study was to compare incidence of pathological fracture due to metastatic bone disease associated with type of lung cancer (LC) according to descriptive data in Prof Dr. dr. IGNG Ngoerah Hospital in 2016-2021

Methods: 21 Patients with lung cancer diagnosed between 2016-2021 in Prof Dr. dr. IGNG Ngoerah hospital. Patient's range of age were 22-81 years old (mean age: 51 yo). Most location of the fracture happened at femur, humerus region. From the pathological examination, we found the type of the lung cancer were Non-Small Cell Lung Carcinoma (Adenocarcinoma).

Results: There were 6 LC patients with MBD was more than 70 years old is affected and patient under than 70 years old is 15 patients. 11 patients were male have bone metastatic bone disease and 10 patient was female. 11 patients have bone metastatic bone disease at femoral, 10 patients consist of the other location group. 12 patients with non-small cell lung carcinoma, and 9 patient without any pathological result.

Conclusions: There are several factors like age, gander, active smoker, length of lung cancer, serum marker, race, geography, socioeconomic statue that related to metastatic bone disease. But in this study, we just found 4 kind of factors like age, gender, pathological result and kind of lung cancer. A further study can improve the interpretation of the results.

Keywords: *Lung cancer, Bone metastatic disease, pathological fracture*

INTRODUCTION

Lung cancer or lung carcinoma is a malignant lung tumor characterized by uncontrolled cell growth in the lung tissues and one of the most common and fatal cancers worldwide among men in most countries and the main cause of cancer death in both sexes. The highest rates are in North America, Europe, and East Asia, with over a one third of new cases in China, it account for 20.6% of cancer mortality. Bone is the common site of distant metastasis in lung cancer. Bone metastases are often complicated with skeletal-related events (SREs) which lead to serious morbidity.

(Malhotra et al. 2016; Mustafa et al. 2016a; Zhou, Chen, et al. 2017)

Bone metastases (BM) represent a common complication of cancer, whose incidence reaches 65–75% in breast cancer (BC), up to 65–90% in prostate cancer (PC) and about 70–95% in multiple myeloma (MM). Skeletal involvement is less frequent in other malignancies, ranging from approximately 10% in colorectal tumors to 17–64% in lung cancer (LC).(D'Oronzo et al. 2019; Zhao et al. 2017). In the 2013-2017 research conducted at Prof Dr. IGNG Ngoerah Hospital, it was found that the incidence of primary tumors that cause metastatic bone disease were breast (6.81%), lung (20.45%), thyroid (13.63%), kidney (2.27%), Prostate (4.45%), unknown origin (31.83%).

The objectives of this study were to determine the association of lung tumor molecular subtypes onsite of metastatic disease and incidence of metastatic bone disease. The determinant factors included age, gander, active smoker, length of lung cancer, serum marker, race, geography, socioeconomic statue.(Malhotra et al. 2016; Mustafa et al. 2016a)

MATERIAL AND METHODS

Patients with breast cancer diagnosed between 2016-2021 in Prof. Dr. IGNG Ngoerah hospital. Patient's range of age were 22-81 years old (mean age: 51 yo). Total 21 patient were diagnosed with lung cancer related metastatic bone diseases.

Most of fracture incidences located at femur (11 cases), followed by humerus, vertebrae, scapula, forearm, hip, and ankle region. From the pathological examination, we found the type of the lung cancer were variative including non-small cell lung carcinoma (adenocarcinoma) and small cell lung carcinoma.

Each patient was graded according to ASA physical status score preoperatively. All patients were operated under regional anaesthesia. Inclusion criteria are patient with lung cancer that having bone fracture due to metastatic process including any kind type of lung cancer's pathological result. Exclusion criteria are if the patient having trauma to the affected area before, and a minimum of 6 months follow-up of the cancer.

At hospital admission; radiographs examination (include antero-posterior and lateral view) of affected area were taken to assess the fractures. If there was no contraindication, all patients underwent operation. Prophylactic third generation cephalosporin (according to their weight) were administered 30 minutes preoperatively. Patients were placed according to procedure approach, respectively depend on location of the fracture. We collect the data of patient that including age, sex, location of the bone fracture, and kind of bone cancer.

RESULTS

Ages

There are conflicting results when analysing the effect of age in the development of BM. The data from 2016-2021 patients with Lung Cancer with MBD at Prof. Dr. IGNG Ngoerah Hospital, the median age of patients who suffering LC with MBD is 51 years old. Some studies have shown that LC patients who develop bone-only metastasis tend to be older than those who relapse with both visceral and bone disease. Patients above 70 years old at diagnosis had a significant decrease in the risk of developing distant metastasis with increasing age.

Study by Bade et al 2020, lung cancer is most common in men and women 70 years of age and older. Lung cancer has become the most common cause of cancer death in men ages 40 and older and women ages 60 and older. The median age at lung cancer diagnosis is 70 years, and the median age at lung cancer death is 72 years. In general, lung cancer mortality increases with age until approximately ages 80 to 85, after which

heart disease exceeds cancer as the most common cause of death in both genders.

From the data in RSUP Prof. Dr. IGNG Ngoerah, from 21 patients, only 8 patients lung cancer with MBD more than 70 years old and 13 patients lung cancer with MBD under 70 years old. The median age is 51 years old. From this data showed patient LC with MBD majority under 70 years old. This is the following diaphragm based on age.

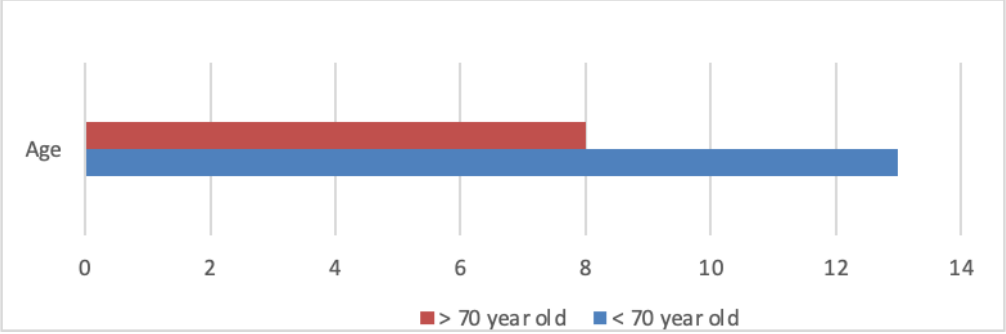


Diagram 1. Patient characteristic based on age

Gender

Gender might also be related to the development of BM in LC patients, men have historically had a much higher incidence of lung cancer than women, the rate in men declined quite dramatically by the end of the twentieth century along with a proportional decline in the male population who smoked. In contrast, lung cancer rates in women have increased since 1965, with a very modest decline only beginning in 2000. Smoking remains prevalent, especially in younger women. In addition, women who do not smoke often become passive smokers of couples who smoke. Women have a higher incidence of adenocarcinoma than squamous cell cancer; 2 to 4 times more often. In addition, women with lung cancer have increased mortality compared to men.

From the data in RSUP Prof. Dr. IGNG Ngoerah, from 21 patients, 12 patients lung cancer with MBD was male and 9 patients lung cancer with MBD was female. From this data showed patient lung cancer with MBD majority was male. This is the following diaphragm based on gender

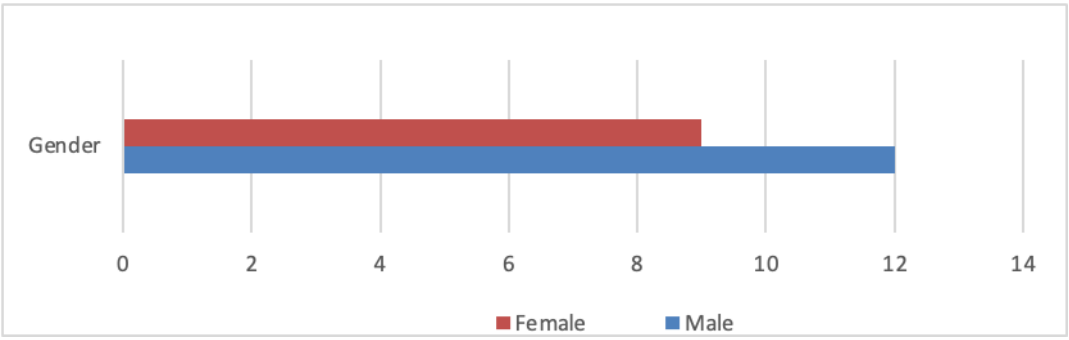


Diagram 2. Patient characteristic based on gender

Pathological result

Pathological analysis is one of the tests that we do for the patient with MBD. The purpose is to investigate that the metastatic were primary or not. We found summary from the pathological data Lung cancer patient with MBD in RSUP Prof. Dr. IGNG Ngoerah, which they are 12 patients with non-small cell lung carcinoma, and 9 patients without any pathological result. From the data shown

above the non-small cell lung carcinoma has the higher incidence to bone metastasis. This is the following diaphragm based on pathological result.

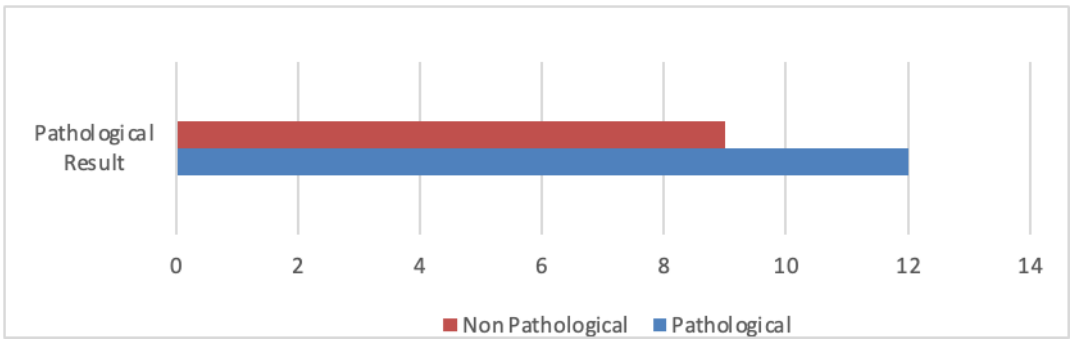


Diagram 3. Patient characteristic based on pathological result

Region

From the data in 21 patients in 2016-2021, 10 patients have metastatic femur region, 5 patients in humerus region, 3 patients in pelvis region, 2 patients in arm region, and 1 patient in humerus region. From the data shown above metastatic to the lower region which is proximal femur and femur is the most metastatic case.

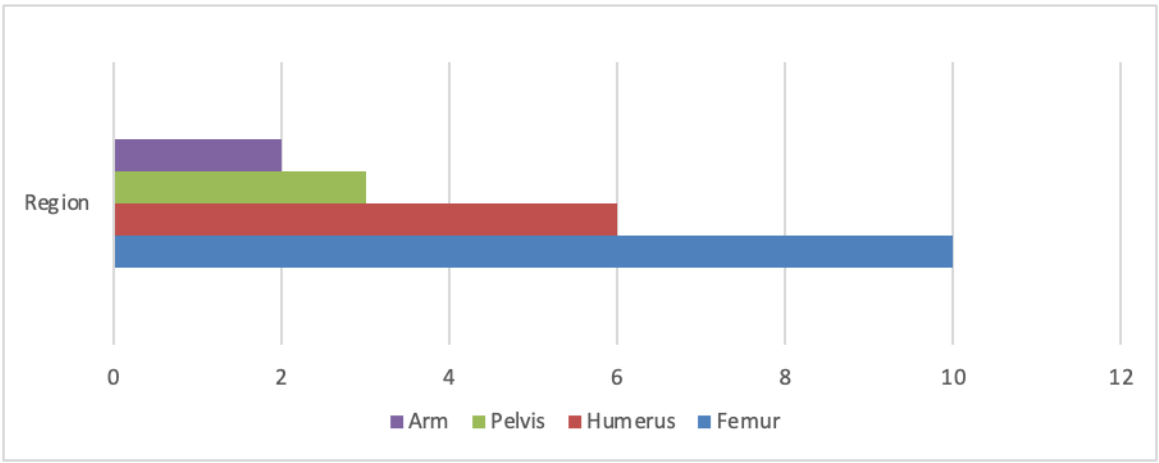


Diagram 4. Patient characteristic based on region

Table of description data

No	Age	Sex	Region	Histology type
1	67	M	Femur dextra	Non-Small Cell Lung Carcinoma cenderung adenocarcinoma
2	61	M	Humerus Dextra	Invasive encapsulated follicular variant of papillary thyroid carcinoma
3	69	F	Femur Sinistra	Metastasis Adenocarcinoma
4	50	F	Femur Sinistra	Metastasis Adenocarcinoma
5	74	F	Femur dextra	Metastasis Adenocarcinoma
6	65	M	Femur dextra	Non-Small Cell Carcinoma
7	48	M	Femur bilateral	(no pathological result)
8	71	M	Femur sinistra	(no pathological result)
9	55	M	Femur dextra	(no pathological result)
10	70	F	Ramus pubis dextra	(no pathological result)
11	67	M	Right Humerus	Non-Small Cell Lung Carcinoma cenderung adenocarcinoma
12	52	F	Femur dextra	(no pathological result)
13	81	M	Left Humerus	Non-Small Cell Carcinoma, cenderung tipe adenocarcinoma
14	75	M	Left Humerus	Non-Small Cell Carcinoma cenderung Adeno Carcinoma

15	68	M	Right Femur	(no pathological result)
16	22	F	Lumbal	(no pathological result)
17	61	F	Right Femur	Adenocarcinoma paru
18	55	F	Left Humerus	(no pathological result)
19	61	F	Ankle Dextra	Metastasis adenocarcinoma
20	57	F	Right humerus	metastasis adenocarcinoma
21	80	M	Left Hip	(no pathological result)

DISCUSSION

Lung cancer or lung carcinoma is a malignant lung tumor characterized by uncontrolled cell growth in the lung tissues. The highest rates are in North America, Europe, and East Asia, with over a one third of new cases in China. The rates in Africa and South Asia are much lower. Pathogenesis in lung cancer is similar to other cancers, lung is initiated by activation of oncogenes or inactivation of tumor suppressor genes. Carcinogens cause mutations in these genes which induce the development of cancer. Mutations in the K-ras proto-oncogene are responsible for 10-30% of lung adenocarcinomas. About 4% of non-small cell lung carcinomas involve an EML4-ALK tyrosine kinase fusion gene. Epigenetic changes-such as alteration of DNA methylation, histone tail modification, or micro-RNA regulation-may lead to inactivation of tumor suppressor genes. Epidermal growth factor receptor (EGFR) regulates cell proliferation, apoptosis, angiogenesis, and tumor invasion. Mutations and amplification of EGFR are common in non-small –cell lung carcinoma and provide the basis for treatment with EGFR-inhibitors, Her2/neu is affected less frequently. Other genes that are often mutated or amplified are c-MET, NKX2-1, LKBI, PIK3CA, and BRAF. The cell lines of origin are not fully understood. The mechanism may involve abnormal activation of stem cells. In proximal airways, stem cells that express keratin 5 are more likely to be affected, typically leading to squamous-cell lung carcinoma. In middle airways, implicated stem cells include club cells and neuroepithelial cells that express club cell secretory protein. Small –cell lung carcinoma may be derived from these cell lines or neuroendocrine cell and may express CD44. Metastasis of lung cancer requires transition from epithelial to mesenchymal cell type. This may occur through activation of signaling pathways such as Akt/GSK3Beta,MEK-ERK, Fas and Par6.(Malhotra et al. 2016)(Zhou, Yu, et al. 2017)

Table 1
Factors influencing likelihood of cigarette smoking

Factor	Those at Highest Risk of Smoking
Gender	Males
Age	Adults <65 y
Race	Non-Hispanic American Indians/Alaska Natives Whites Blacks Multiracial adults
Geography	South Midwest
Education	Those with a General Education Development certificate
Income	<$35,000/y
Sexual orientation	Lesbian, gay, or bisexual adults
Marital status	Divorced, separated, widowed Single, never married, or not living with a partner
Insurance	Uninsured Insured by Medicaid or other public insurance (not Medicare)
Comorbidities	Adults with a disability or serious psychological distress

From Wang TW, Asman K, Gentzke AS, et al. Tobacco Product Use Among Adults - United States, 2017. MMWR Morb Mortal Wkly Rep 2018;67(44):1225-1232.

Table 1. Risk Factor for Lung Cancer.(Bade and Dela Cruz 2020)

Cancer staging is a critical step in the diagnosis process, and its objectives are multifarious including : (Zhou, Chen, et al. 2017)

1) Helping the clinician to recommend a treatment plan;
2) Giving some indication of prognosis;
3) Aiding in the evaluation of the results of treatment;
4) Facilitating the exchange of information between treatment centers;
5) Contributing to the continuing investigation of human cancer.

The international TNM-based staging system describes the anatomical extent of the disease. The T category describes the size and extent of the primary tumor. The N category describes the extent of involvement of regional lymph nodes. The M category describes the presence or absence of distant metastatic spread. The addition of numbers to these categories describes the extent of the cancer. All possible combinations of the T, N, and M categories are then used to create TNM subsets. TNM subsets with similar prognoses are then combined into stage groupings. NSCLC stages range from one to four (I through IV). The lower the stage, the less the cancer has spread. SCLC is defined using two stages: Limited (confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes) and extensive (spread beyond the supraclavicular areas).
(Bade and Dela Cruz 2020; Zhou, Chen, et al. 2017)

The term stage, without further classification, relates to the pretreatment, clinical stage or cTNM. cTNM is derived using the evidence available from clinical history and examination, blood tests, imaging, endoscopic examination, biopsy material, surgical examination, and any other test considered necessary prior to making a decision as to the appropriate treatment in any individual. If this decision leads to surgical treatment, then additional information becomes available at surgery and by pathological examination allowing a more accurate assessment of disease indicated by the pathological, postsurgical stage or pTNM. pTNM does not replace the cTNM, which should remain as a record in the patient's notes. If the patient undergoes preoperative "induction" therapy, usually with either or both chemotherapy and radiotherapy, then a reassessment is made after this treatment, prior to a final decision on surgical treatment. The evidence available from this process is used to create the ycTNM, and after surgical treatment in these circumstances, the postsurgical pathological extent of disease is described as ypTNM. At various points in the patient's journey, events may allow or demand a reassessment of disease extent. An rTNM may be established if relapse occurs after a disease-free interval. An aTNM may be formulated if the disease is first discovered at an autopsy. In each case, previous assessments of TNM are retained in the patient records.(Mustafa et al. 2016b; Zhou, Chen, et al. 2017)

Factors	BM	NBM	*p* value
Gender			0.551
Male	195	644	
Female	69	207	
Age (years)	59.77 ± 11.05	61.86 ± 9.69	0.006
Histopathology			<0.001
Adenocarcinoma	158	316	
Squamous cell carcinoma	57	341	
Small-cell lung cancer (SCLC)	28	138	
Poorly differentiated	12	19	
Large-cell carcinoma	2	4	
Adenosquamous carcinoma	1	2	
Others	6	31	
CYFRA21-1 (ng/mL)	14.21 ± 35.23	9.55 ± 28.55	0.051
NSE (ng/mL)	39.18 ± 62.18	29.16 ± 40.21	0.018

BM: bone metastasis; NBM: non bone metastasis; NSE: neuron-specific enolase.

Table 2. Risk Factor of lung cancer related to bone metastasis.(Zhou, Chen, et al. 2017)

Cancer develops following genetic damage to DNA and epigenetic changes. These changes affect the normal functions of the cell, including cell proliferation, programmed cell death (apoptosis) and DNA repair. As more damage accumulates, the risk of cancer increases : (Ahmad and Mayya 2020; de Groot and Munden 2012; Mustafa et al. 2016a)

1. Gender

Lung cancer incidence and mortality are consistently lower in women compared with men. the demographics of women diagnosed with lung cancer are different than those in men. Specifically, women tend to be diagnosed with lung cancer at a younger age, are more likely to be nonsmokers, and are more likely to be diagnosed with an adenocarcinoma. Finally, women have improved lung cancer survival across all disease stages than men. In combination, these findings support unique biological and genetic mechanisms of lung cancer between men and women.(Bade and Dela Cruz 2020)

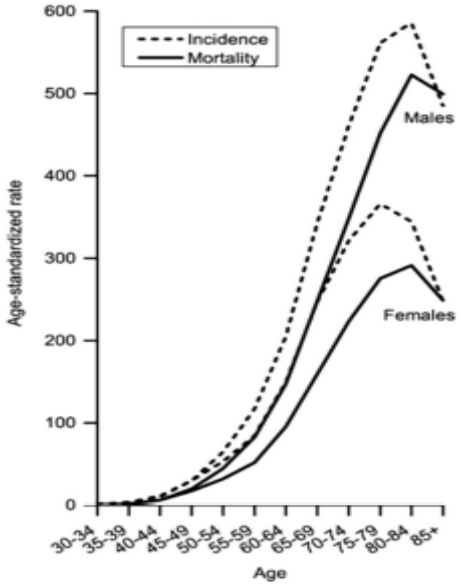


Table 3. Gander as risk factor of lung cancer.(de Groot and Munden 2012)

2. Age

Lung cancer is most common in men and women 70 years of age and older. Lung cancer has become the most common cause of cancer death in men ages 40 and older and women ages 60 and older. The median age at lung cancer diagnosis is 70 years, and the median age at lung cancer death is 72 years. In general, lung cancer mortality increases with age until approximately ages 80 to 85, after which heart disease exceeds cancer as the most common cause of death in both genders. Interestingly, a recent study identified higher incidence rates of lung cacer among young Hispanic and non-Hispanic white women (compared with men) between the ages of 30 and 49 years. Although smoking patterns likely contribute to this finding, the authors noted that smoking behaviors did not entirely explain the recognized differences. The discovery of higher incidence of lung cancer in younger women demonstrates how our “traditional” view of lung cancer is changing.

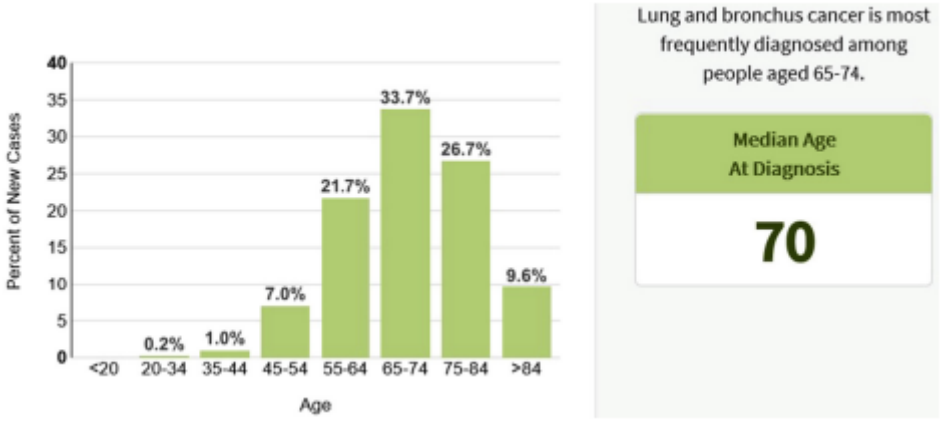


Table 4. Age as risk factor of lung cancer.(de Groot and Munden 2012)

3. Active smoker

Tobacco use in the form of cigarettes has significantly increased with the average adult smoking. Fewer than 100 cigarettes per year in the 1900s to the estimated maximum of approximately 4400 cigarettes per person per year in them 1960s. The seminal US Public Health Service report by the Surgeon General in 1964 was instrumental in highlighting the adverse effects of cigarette smoking on health, concluding that cigarette smoking was associated with a 70% increase in the age-specific death rates for men, a lesser increase in the death rates for women, and that cigarette smoking was causally related to lung cancer. Moreover, cigarette smoking was believed to be more important than occupational exposures in the cause of lung cancer. Since the report, smoking has decreased from 20.8% of all US adults aged 18 years or older in 2005 to 14.0% in 2017. The proportion of ever smokers that have quit has also increased.

4. Length of lung cancer

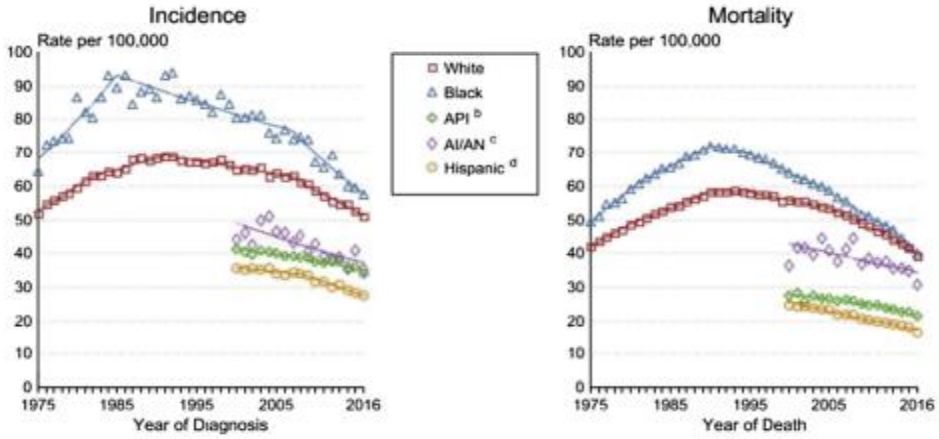
In some journal show that length of cancer can related to higher risk for bone metastatic disease, but this statement needs further examination.

5. Serum marker

Serum marker is the important rule for identified cancer, in normal condition serum marker such as CEA, Ca19.9 was in normal limit, but when in there is any abnormalities in bodies (when cell growing abnormal) serum marker was growing higher.

6. Race

Lung cancer incidence and mortality are highest in African American men and lowest in Hispanic women. In data from 2008 to 2014, compared with Caucasians, African Americans had lower rates of localized disease at diagnosis (13% vs 17%) and worsened 5-year relative survival for localized (52% vs 56%), regional (27% vs 30%), and all-stage disease (16% vs 19%). Higher lung cancer-associated mortality by race is likely multifactorial, including smoking prevalence, access to health insurance, and SES. American Indians/Alaska Natives currently have the highest overall smoking rate in the United States (21.9%). Whereas lung cancer mortality has been decreasing in most races since the early 1990s, lung cancer mortality in American Indians and Alaska Natives did not start falling until approximately 2010.



7. Geography

Geography influences lung cancer epidemiology in the United States, and smoking patterns determine the higher and lower risk areas. Currently, the highest lung cancer incidence and mortality rates are in Kentucky, where the age-adjusted incidence per 100,000 people is 112.8 for men and 79.0 for women. The age-adjusted mortality per 100,000 people in 84.5 in men and 52.2 in women. In contrast, the lowest incidence and age-adjusted lung cancer death rates are in Utah, with incidences of 32.4 and 23.7 and mortality rates of 23.4 and 15.6 in men and women, respectively. Although lung cancer incidence and mortality rates are decreasing nationally, several areas of the country with higher smoking prevalence have not observed the same improvements in lung cancer outcomes.

8. Socioeconomic statue

Lower SES and education contribute to lung cancer risk and worse outcomes, particularly in men. Men and women with less than a high school education or annual incomes of less than $12,500 and with lower SES including educational, occupational, and income-based positions have higher lung cancer rate ratios. Because lower income counties have much higher rates of tobacco smoking, lung cancer disparities owing to SES are analogous to those seen geographically. In poor counties (compared with affluent counties), lung cancer mortality in men is more than 40% higher, and low SES may increase the risk of death during hospitalization for a lung cancer resection. However, studies have shown that controlling for education, SES, and smoking status decreased but did not normalize lung cancer risk. It seems clear that the individual's risk of developing and surviving lung cancer is the result of a complex relationship involving age, gender, race, smoking status, geographic location, and SES

CONCLUSIONS

There are several factors like age, gander, active smoker, length of lung cancer, serum marker, race, geography, socioeconomic statue that related to metastatic bone disease. But in this study, we just found 4 kind of factors like age, gender, pathological result and kind of lung cancer. A further study can improve the interpretation of the results.

Declaration by Authors

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