

RISK FACTORS OF LUNG ADENOCARCINOMA IN PATIENTS AT DR. SOETOMO DISTRICT GENERAL HOSPITAL SURABAYA IN 2018

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ABSTRACT

Lung adenocarcinoma is one type of lung cancers that increases in number every year globally. Smoking is one of the risk factors for lung adenocarcinoma. This study aimed to determine the distribution of the risk factors of lung adenocarcinoma in patients. The risk factors observed in this study included age, gender, smoking history, number of cigarettes, types of cigarettes, and smoking duration. This study was descriptive and performed a cross sectional design. The study's population was all lung cancer patients who were treated at Dr. Soetomo District General Hospital Surabaya. The samples were drawn using the accidental sampling technique from the population that met the inclusion criteria. The inclusion criteria for this respondents were patients who were diagnosed with lung adenocarcinoma and were willing to be interviewed. While the exclusion criteria involved patients with incomplete medical record data and patients who were not willing to be interviewed. The results indicate that the majority of lung adenocarcinoma patients at Dr. Soetomo District General Hospital Surabaya were male who were light smokers, diagnosed at more than 50 years old. Most of them used filter cigarettes and had smoked for more than 30 years.

Keywords: Lung adenocarcinoma, risk factors

ABSTRAK

Adenokarsinoma paru merupakan salah satu jenis kanker paru yang jumlahnya meningkat setiap tahunnya di seluruh dunia. Penggunaan rokok merupakan salah satu faktor risiko dari adenokarsinoma paru. Penelitian ini bertujuan untuk mengetahui distribusi faktor risiko adenokarsinoma paru pada pasien. Faktor risiko yang diteliti, yaitu usia saat diagnosis, jenis kelamin, riwayat merokok, jumlah batang rokok, jenis rokok, dan lama merokok. Penelitian ini adalah penelitian deskriptif observasional dengan desain potong lintang (cross sectional). Populasi pada penelitian ini adalah seluruh pasien kanker paru yang berobat di RSUD Dr. Soetomo Surabaya tahun 2018. Sampel penelitian berasal dari populasi yang dipilih menggunakan teknik sampling aksidental sesuai dengan kriteria inklusi. Kriteria inklusi penelitian ini adalah pasien yang didiagnosis kanker paru jenis adenokarsinoma dan bersedia diwawancarai. Sedangkan kriteria eksklusi penelitian ini adalah pasien yang data rekam mediknya tidak lengkap dan pasien yang tidak bersedia diwawancarai. Hasil menunjukkan bahwa pasien adenokarsinoma paru yang berobat di RSUD Dr. Soetomo Surabaya sebagian besar adalah laki-laki, didiagnosis kanker paru saat berusia 50 tahun atau lebih, dan perokok ringan. Kebanyakan menggunakan jenis rokok filter dan telah merokok selama 30 tahun atau lebih.

Kata kunci: Adenokarsinoma paru, faktor risiko

INTRODUCTION

Lung cancer is a type of cancer that causes deaths in the world (Putra et al., 2015). The highest new lung cancer cases

occur to 30% of male population and has caused 34.2% deaths worldwide. In female population, the lung cancer cases reach 13.6% and has caused 11.2% deaths (GLOBOCAN, 2012).

The incidence of lung cancer in men in Indonesia reached 25,332 cases and caused 21.8% deaths of 103,100 people with cancer. The incidence of lung cancer was three times less in women, amounting to 9,374 cases with a mortality rate of 9.1% of 92,200 people with cancer (WHO, 2014).

Carcinogen is a chemical which makes the growth of lung cells out of control, thereby causing lung cancer. Based on its histology, lung cancer has two types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Non-small cell lung cancer (NSCLC) is the most common type, and it is classified into three main subtypes: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma (Clarke, 2017).

Recent lung cancer trends show an increased incidence of pulmonary adenocarcinoma in men and women, as previously observed in the United States (Paris, et al. 2010). Data from the Southeast Asia Tobacco Control Alliance (2017) show that the incidence of pulmonary adenocarcinoma in Southeast Asia tend to increase in recent years compared to other types of lung cancer. Research conducted by Wang, et al. (2014) at the Guangzhou Medical College Hospital shows that the proportion of pulmonary adenocarcinomas in 61 lung cancer patients (55.7%) was higher than other types of non-small cell lung cancer.

Severe lung tumor is most likely to spread to the central nervous system (CNS). As many as 50% of patients diagnosed with NSCLC or SCLC will experience metastases in the brain. Interestingly, different lung cancer subtypes spread to the CNS at different rates. CNS metastases mostly occur in patients with pulmonary adenocarcinoma compared to patients with other non-small cell lung cancers (6.6 - 43%). CNS metastases cause not only the clinical burden of morbidity and mortality, but also acute neurological deficits, cognitive impairment, and seizures (Wang, et al. 2014).

According to Mäkinen (2017), since the 1960s, the increased incidence of pulmonary adenocarcinoma has been linked to three factors related to smoking. The first factor is a change in cigarette production with the appearance of filter cigarettes, containing lower tar and nicotine and thus leading to deeper smoke inhalation and the spread of tobacco smoke to the lungs. It occurs due to the increase in tobacco-specific N-nitrosamines transforming central tumors (including squamous cell carcinoma (SCC) and small cell lung cancer (SCLC)) to peripheral tumors or lung adenocarcinoma (Travis, et al. 2015). The second factor is the risk of SCC and SCLC increasing rapidly with more increasing smoking duration than that of pulmonary adenocarcinoma which appears later (Lortet-Tieulent, et al. 2014). The third factor is reduced risk of SCC and SCLC after stopping smoking than that of adenocarcinoma (Kenfield, et al. 2008).

Evidence shows that non-smoking factors also influence changes in the prevalence of pulmonary adenocarcinoma (Lee, et al. 2016). An estimated 10-15% of lung cancer deaths are caused by factors in spite of active smoking (Samet, et al. 2009). Improvements in imaging and detection of peripheral pulmonary nodules, as well as changes in the classification of lung tumor histology and pathology may have influenced the time trend in the ratio of pulmonary adenocarcinoma to SCC (Lee, et al. 2016). The prevalence pulmonary adenocarcinoma is always higher than that of SCC in women regardless of smoking status (Samet, et al. 2009).

The incidence of lung cancer can be controlled by establishing a diagnosis as early as possible. Histopathological examination of the type of lung cancer is also important to do to help the doctor determine the therapy to be given. Much analysis is needed on the risk factors that influence types of lung cancer, especially those related to smoking behavior, such as smoking history, smoking duration, types of cigarettes, and the number of cigarettes.

This study aimed to determine the distribution of risk factors of pulmonary adenocarcinoma in patients at Dr. Soetomo District General Hospital Surabaya in 2018. It is expected to increase knowledge about risk factors for pulmonary adenocarcinoma as a basis for determining prevention and control measures for lung cancer.

METHODS

This study was an observational-descriptive study with a cross-sectional study design. Data were collected in November 2018 at Dr. Soetomo District General Hospital Surabaya. The study's population was all lung cancer patients treated at the hospital in 2018. The research sample was selected using the accidental sampling technique from the population that fits the inclusion criteria. They were patients who were diagnosed with adenocarcinoma lung cancer and were willing to be interviewed. While patients with incomplete medical records and those who were not willing to be interviewed were excluded from the sample.

This study used primary data and secondary data. Primary data were questionnaire-based interviews with patients, while secondary data were obtained by looking at the patients' medical record data.

Independent variables observed included age at diagnosis, sex, smoking history, number of cigarettes, types of cigarettes, and smoking duration. Furthermore, the study's dependent variable was the incidence of pulmonary adenocarcinoma.

This study has obtained an ethical approval by the Ethics Committee of Dr. Soetomo District General Hospital Surabaya on October 14th, 2018, with No. 0727 / KEPK / X / 2018.

RESULTS

This study presents the distribution of risk factors of pulmonary adenocarcinoma in Table 1. It shows that the number of male patients (55.6%) was more than that of female patients (44.4%). The table also explains that most patients (66.7%) who were diagnosed with cancer were 50 years old or older.

Additionally, smoking history variable is categorized into active smokers, passive smokers, and nonsmokers. Active smokers are respondents who have smoked at least 100 cigarettes during their lives, and passive smokers are non-smokers who are exposed to cigarette smoke in the environment. While nonsmokers are respondents who have smoked less than 100 cigarettes or never smoked during their life. The results indicate that the number of patients who were active smokers were more dominant (52.8%) than that of passive smokers (19.4%) and non-smokers (27.8 %).

Of the 19 active smokers, 14 of them (73.7%) had smoked for 30 years or more, and 5 patients (36.3%) had smoked for less than 30 years. These data indicate that the majority of pulmonary adenocarcinoma active smokers had smoking duration of 30 years or more.

In terms of types of cigarettes, patients were considered to smoke non-filter cigarettes if they consumed weekly more than 50% of cigarettes which do not have cork or synthetic fiber foam . While some were considered to take filter cigarettes if they smoked weekly more than 50% of cigarettes with cork or synthetic fibers foam. Out of 9 active smokers, there were 7 patients (36.8%) who smoked non-filter cigarettes and 12 patients (63.2%) who smoked filter cigarettes. In other words, pulmonary adenocarcinoma patients who were active smokers mostly smoke filter cigarettes.

Table 1. Distribution of Lung Adenocarcinoma Risk Factors at Dr. Soetomo General District Hospital in 2018.

Variable	Category	Frequency (n)	Percentage (%)
Gender	Female	16	44.4
	Male	20	55.6
	Total	36	100.0
Age at Diagnosis	≥50 years	24	66.7
	<50 years	12	33.3
	Total	36	100.0
Smoking History	Active smokers	19	52.8
	Passive smokers	7	19.4
	Non-smokers	10	27.8
	Total	36	100.0
Smoking Duration	≥30 years	14	73.7
	<30 years	5	26.3
	Total	19	100.0
Types of Cigarettes	Non-Filter	7	36.8
	Filter	12	63.2
	Total	19	100.0
Number of Cigarettes	Light	19	52.8
	Moderate	8	22.2
	Weight	9	25.0
	Total	36	100.0

This study also grouped the patients into light smokers, moderate smokers, and heavy smokers. Light smokers are patients who have a Brinkman index value of 0-199 points, and moderate smokers are those with a Brinkman index value of 200-599 points. Further, heavy smokers are patients who have a Brinkman index value of more than 600 points. Brinkman index is calculated by multiplying the average number of cigarettes smoked everyday and smoking duration every year. The results show there were 19 light smokers (52.8%), 8 moderate smokers (22.2%), and 9 heavy smokers (25.0%). It means the majority of pulmonary adenocarcinoma patients were light smokers.

DISCUSSION

Based on gender, the majority of pulmonary adenocarcinoma patients were male. A recent analysis of trends in lung cancer incidence in Europe has shown that

the incidence of pulmonary adenocarcinoma was increasing in both men and women and had no relationship between gender (OR = 1.13 [95 % CI: 0.78 - 1.63]) (Paris, et al, 2010). It is in contrast to Hernowo's research (2012) which shows that the prevalence of pulmonary adenocarcinoma in men was 25%, which was lower than in women at 42%. Women are more at risk of suffering from pulmonary adenocarcinoma as they are vulnerable to carcinogens of tobacco smoke. The increased incidence of pulmonary adenocarcinoma in women may be closely related to specific risk factors of lung cancer among women, such as hormonal factors or gene susceptibility (Paris, et al, 2010).

According to Cooper, et al. (2013), almost all Epidermal Growth Factor Receptor (EGFR) mutations occur to pulmonary adenocarcinoma patients. EGFR gene mutations are more commonly found in female patients, young patients, and non-

smoker patients. Oktavianti (2015) discovers female patients with lung adenocarcinoma experienced EGFR mutations more. Also, EGFR mutations occurred to nonsmokers (51%) than active smokers (10%).

Supporting this study finding about age of lung cancer patients, Roszkowski (2001) also discover the incidence of pulmonary adenocarcinoma was higher in patients diagnosed with lung cancer at less than or equal to 50 years (12.6%) than patients diagnosed at more than 50 years of age (7.6%). The same results were obtained by Guntulu, et al. (2007) who find that 23.5% pulmonary adenocarcinoma incidence occurred to patients under 50 years old, while 17.8% were observed in patients aged 50 years or more. Some studies argue that differences in age where patients are diagnosed with lung cancer have something to do with smoking characteristics.

Furthermore, most of the patients with pulmonary adenocarcinoma are active smokers. Wakelee, et al. (2007) further elaborate the highest proportion of pulmonary adenocarcinoma incidence occurs to non-smokers, while the medium proportion is discoverable in former smokers. Whereas the lowest proportion is observed among heavy smokers. Lung adenocarcinoma is known a cancer type discovered in non-smokers, but the proportion does not give overview about the risks of pulmonary adenocarcinoma between smokers and nonsmokers.

Biological pathways that include extracellular matrix-receptor interaction, as well as migration and cell proliferation, affect the incidence of lung cancer, regardless of smoking status. However, smoking induces unique gene expression patterns as seen in the increase in cell cycle regulators (CDK1, CCNB1, and CDC20). Biological pathway and p53 signaling pathway significantly influence biological tissue as well. This finding provides a better understanding of how smoking causes the molecular changes that contribute to the

pathogenesis of pulmonary adenocarcinoma (Hu and Chen, 2015).

Cigarette smoke contains several classes of carcinogens such as polycyclic aromatic hydrocarbons, benzo (a) pyrenes, and tobacco-specific nitrosamines. Most of these compounds exert their genotoxic effects by forming DNA and reactive oxygen species that can cause mutations in the K-RAS and p53 genes. Tobacco-specific nitrosamines can also activate nicotinic acetylcholine receptors (nAChR) and b-adrenergic receptors (b-AR) to some extent. The activation of these receptors can cause cell proliferation. Furthermore, it has been proven that nicotine is a major addictive component of cigarette smoke that can trigger the development of cell cycles, angiogenesis, and metastases of lung and pancreatic cancer (Schaal and Chellappan, 2014).

There are unique patterns of gene expression, especially in lung cancer patients with a history of smoking. These patterns include CDK1, CCNB1, STAT1, AURKA, and CDC20. All the Differentially Expressed Genes (DEG) encode important regulators that determine the control and development of the cell cycle, which shows that smoking triggers cell hyperproliferation which contributes to the pathogenesis of pulmonary adenocarcinoma. Many previous studies have stated a strong relationship between smoking and cell proliferation in various types of malignancies, including lung cancer. Mitogenic effects are largely mediated by nicotine and its derivatives through a variety of different molecular mechanisms. For example, smoking induces radical oxygen production which causes the formation of truncated amphiregulin transmembrane, which is then detected by EGFR and results in the proliferation of aberrant pulmonary epithelial cells. Besides, by involving nicotinic acetylcholine receptors (nAChR), nicotine provides pleiotropic cellular functions for growth factor secretion (such as VEGF and platelet-derived growth

factor) and initiation of mitogen-activated protein kinase signaling. Specifically, in non-small cell lung cancer, nAChR activation induces the recruitment of β -arrestin to the receptor, which in turn activates Src and increases the binding of E2F1 and Raf-1 transcription activators to the proliferative promoter. Consequently, exposure to nicotine of cigarettes prompts abnormal mitogenesis through various mechanisms that contribute synergistically to the initiation and development of pulmonary adenocarcinoma (Hu and Chen, 2015).

With smoking duration of more than or equal to 30 years among patients in this study, it indicates that smoking causes addiction. Ji, et al. (2015) assert smoking duration is associated with the dose-response to nicotine that affects body parts prone to lung cancer risk, including chromosome 15q25 which contains several genes that play a role in cell growth, signaling, and metabolism. Chromosome 15q25 contains the nicotinic acetic acid receptor (CHRNA5-CHRNA3-CHRNA4) involved in the process of nicotine addiction. It mediates the synthesis and release of growth factors and signals the growth of tumors and metastasis. Additionally, chromosome 15q25 is also associated with peripheral arterial disease and chronic obstructive pulmonary disease (COPD) (Koifman, et al., 2009).

In this study, most of the patients with pulmonary adenocarcinoma smoked filter cigarettes. In similar way, Marugame, et al. (2004) have found that the risk of pulmonary adenocarcinoma was higher in filter smokers compared to non-filter smokers, regardless of gender. Supporting this finding, Ombao, et al. (2010) further describe filter cigarettes were more likely to contribute to the increased incidence of pulmonary adenocarcinoma.

Filter cigarettes produce deep and intense tobacco smoke inhalation and transmit larger carcinogens such as nitrogen oxides and nitro salty compounds to the lung edges. It has been hypothesized that

the upward trend in pulmonary adenocarcinoma is mainly due to the spread of filter cigarettes. People inhaled filter cigarettes more deeply than non-filter cigarettes. The inhalation transports tobacco-specific carcinogens further towards the bronchioalveolar junction, a place where pulmonary adenocarcinoma often appears (Ombao, et al. 2010).

Concerning types of smokers, the majority of pulmonary adenocarcinoma patients observed in this study were light smokers who had consumed 0-199 cigarettes during their lifetime. To further explain this finding, Seki, et al. (2013) explain that the risk of pulmonary adenocarcinoma would increase 2.82 times in men who smoked 21 cigarettes per day or more (95% CI: 2.00 - 3.98). In men who smoked 11-20 stems per day, the risk would increase by 2.06 times (95% CI: 1.51 - 2.81).

CONCLUSION

This study concludes that lung adenocarcinoma patients at Dr. Soetomo Surabaya were predominantly male, diagnosed with cancer at the age of 50 years or older. Most of them were light smokers who smoked 0-199 cigarettes during their lifetime for 30 years or more, and the majority smoked filter cigarettes.

This study recommends smoker to educate the community about the dangers of smoking, especially emits effects on non-smokers. Also, the provision of smoking cessation service integrated with disease control in health facilities is important for stopping people to smoke. It is expected to reduce the risk factors of lung cancer as most lung cancer patients are smokers.

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