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Research Article

Risk Factors for Lung Cancer in Non-smoking Women, North Sumatera, Indonesia

Indra Buana[1], Noni Novisari Soeroso[*2], Setia Putra Tarigan[2], Elisna Syahruddin[3]
[1]*Department of Pulmonology & Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara/Adam Malik General Hospital, Medan, 20155, Indonesia*
[2]*Department of Pulmonology & Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara/Prof. Dr. Chairuddin P. Lubis USU Hospital, Medan, 20155, Indonesia*
[3]*Department of Pulmonology & Respiratory Medicine, Faculty of Medicine, Universitas Indonesia/Persahabatan Hospital, Jakarta, 16424, Indonesia*
[*]Corresponding Author: noni@usu.ac.id

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ABSTRACT

Background: Basic Health Research Data in 2018 reported that lung cancer in women in Indonesia ranked third after breast cancer. A person's risk of developing lung cancer can be evaluated by looking at age, genetic predisposition, tobacco use, and exposure to toxic agents. **Objective:** To obtain data on several risk factors associated with the incidence of lung cancer in non-smoking women at Adam Malik General Hospital and Santa Elisabeth General Hospital. **Methods:** This case-control matching study involved 224 research subjects through medical record data collection from January 2019 to December 2020. All subjects were confirmed by questionnaires related to risk factors: age, exposure to cigarette smoke (passive smokers), genetics, exposure to firewood, and air pollution. Data were analyzed by logistic regression test. **Results:** The average age in the case group was 57.86 years; in the control group, 47.4 years. Five risk factors influenced lung cancer incidence: age ($p = 0.008$), passive smokers ($p = 0.043$), genetic factors ($p < 0.001$), exposure to firewood ($p = 0.007$), and air pollution ($p = 0.041$). **Conclusion:** Risk factors that significantly influence lung cancer incidence in non-smoking women are age over 40 years, genetic factors, passive smoking, and exposure to firewood.

Keywords: lung cancer, non-smoker, risk factors, women

1. Introduction

Lung cancer is the most common type of cancer in both men and women, with high morbidity and mortality rates. According to the American Cancer Society in 2020, lung cancer ranks second after colon cancer as the cause of cancer in the world. The prevalence of lung cancer in men is 116,300 people and in women 112,520 people with a death rate of up to 135,720 people per year [1].

Lung cancer is estimated at 2.2 million new cancer cases and 1.8 million deaths, lung cancer is the second most commonly diagnosed cancer and the leading cause of lung cancer deaths in 2020 around 11.4% of cancers. Lung cancer is the main cause of cancer morbidity and mortality in men while in women it ranks third after breast and colorectal cancer and the second leading cause of death after breast cancer [1-5].

This number shows an increase in the incidence of lung cancer in women compared to 2019, it is said that smoking is no longer the only cause of lung cancer. In addition, in the research of Couraud et al., the incidence of lung cancer in the non-smoking population increased in the range of 10-25% [2].

The incidence of lung cancer in women continues to increase every year. The latest research has shown an increase in number the incidence of lung cancer in women who have never smoked. The existence of risk

factors for lung cancer in women is im portant in prevention and diagnosis efforts. In addition to cigarettes, other risk factors that have been reported are exposure to environmental cigarette smoke, exposure to biomass smoke, exposure to radon, asbestos, heavy metals, infections, genetics, and others [3].

A person's risk of developing lung cancer can be evaluated by looking at several things, namely age and gender factors, genetic predisposition to cancer, tobacco use, and exposure to toxic agents at home or work. Many individuals only have one risk factor, but some other individuals have more than one risk factor, and there are also some patients whose cause of cancer is unknown [4].

Although the majority of lung cancers are associated with tobacco smoke, 25% of lung cancers worldwide occur in people who have never smoked, especially in Asian countries. From these data, the majority of patients who have never smoked are known to have lung cancer with adenocarcinoma histopathology type and are from East Asian ethnicity [2, 6].

Previously, there had been research on the incidence of lung cancer in male active smokers, lung cancer in female active smokers, and lung cancer in female non-smokers. There had even been previous research reporting that there was an increase in the incidence of lung cancer among female non-smokers in North Sumatra [7]. Therefore, researcher is interested in studying the incidence of lung cancer in non-smoking women associated with several risk factors at Adam Malik General Hospital Medan and Santa Elisabeth Hospital Medan.

2. Methods

This was a descriptive study with cross-sectional design and simple random sampling. Samples were This is a case-control matching study involving 224 research subjects through medical record data collection at Adam Malik General Hospital Medan and Santa Elizabeth Hospital Medan from January 2019 to December 2020. All research subjects were recorded from medical record data and confirmed with a questionnaire related to risk factors, namely age, exposure to cigarette smoke (passive smokers), genetics, mosquito coils, limes, pesticides, burning garbage, exposure to firewood, and air pollution. This research with inclusion criteria in the case sample group is patients diagnosed with lung cancer that has been diagnosed based on cytology/histopathology examination in non-smoking women patients and exclusion criteria in the case sample group are patients who are smokers or have a history of smoking. In contrast, the inclusion criteria in the control sample group are patients who are diagnosed with lung cancer in non-smoking women patients, and exclusion criteria in the control sample group are patients who are smokers and have a history of smoking. Data was analyzed by logistic regression test. This research has been approved by the ethics committee.

3. Results

Based on the frequency distribution of age in this study, the average age in the case group was 57.86 years with the youngest age of 24 years and the oldest age of 87 years. Meanwhile, the control group with an average age of 47.4 years with the youngest age of 18 years and the oldest age of 86 years. The largest age group in the two study groups was aged ≥ 40 years, totaling 107 people (95.5%) in the case group and 82 people (73.2%) in the control group. In the case group, there were 107 people (95.5%) aged ≥ 40 years while in the control group subjects aged ≥ 40 years were 82 people (73.2%). Using the Chi-Square test showed that there was a significant relationship between age and the incidence of lung cancer in women who were not smokers ($p < 0.001$). This is in line with research conducted by Kim et al. in Korea reporting the number of women who were not smokers who experienced lung cancer at the age of 55 to 79 years [8]. The research is also by a large study conducted by Wakele in 2007, namely that the incidence rate of lung cancer in women who never smoked aged 40 to 79 years ranged from 14 to 21 cases per 100,000 people per year [9]. All subjects included in this research met the inclusion criteria. Subject characteristics are presented in Table 1.

Table 1. Characteristics of research subjects

Subject Characteristics	Cases (n =112)	Control (n = 112)
Age, years		
Mean (SD)	57.86 (10.67)	47.4 (14.07)
Median (Min-Max)	58.5 (24 – 87)	48.5 (18 – 86)
≥ 40 years	107 (95.5)	82 (73.2)
< 40 years	5 (4.5)	30 (26.8)
Tribe, n (%)		
Aceh	8 (7.1)	5 (4.5)
Batak	61 (54.5)	67 (59.8)
Java	35 (31.2)	34 (30.4)
Mandailing	2 (1.8)	0
Malay	1 (0.9)	3 (2.7)
Minang	1 (0.9)	3 (2.7)
Chinese	4 (3.6)	0
Type of Carcinoma, n (%)		
Adenocarcinoma	105 (93.8)	0
Squamous cell carcinoma	7 (6.3)	0
Stadium, n (%)		
Stage III	4 (3.57)	0
Stage IV	108 (96.43)	0

The average age in the case group was 57.86 years, with the youngest being 24 and the oldest being 87. Meanwhile, in the control group, the average age was 47.4 years, with the youngest being 18 and the oldest being 86. The largest age group in the two study groups was aged ≥ 40, totaling 107 people (95.5%) in the case group and 82 people (73.2%) in the control group.

The largest tribe in the two groups is the Batak tribe, there are 61 people (54,5%) in the case group and 67 people (59.8%) in the control group. The second largest ethnic group in the two groups is Javanese, totaling 35 people (31.2%) in the case group and 34 people (30.4%) in the control group. Table 2 shows the results of the analysis of the relationship between risk factors and the incidence of lung cancer in women who are not smokers.

Table 2. Relationship of Risk Factors with Lung Cancer Incidence in Non-Smoking Women

Risk Factors	Case (n = 112)	Control (n = 112)	P-value	OR (95% CI)
Age, n (%)				
≥ 40 years	107 (95.5)	82 (73.2)	<0.001[a]	7,829
< 40 years	5 (4.5)	30 (26.8)		(2,911-21,060)
Passive Smokers, n (%)				
Yes	84 (75)	70 (62.5)	0.044[a]	1,800
No.	28 (25)	42 (37.5)		(1,014-3,195)
External Tobacco Exposure House, n (%)				
Yes	82 (73.2)	68 (60.7)	0.047[a]	1,769
No	30 (26.8)	44 (39.3)		(1,006-3,110)
Duration of exposure at home, n (%) > 10 years				
Yes	71 (86.6)	38 (55.9)	<0.001[a]	5,096
No	11 (13.4)	30 (44.1)		(2,300-11,287)
Work Environment, n (%)				
Yes	20 (17.9)	12 (10.7)	0.127[a]	1,812
No	92 (82.1)	100 (89.3)		(0.839-3.911)

Duration of Occupational Exposure, n (%) < 10 years				
Yes	14 (70)	9 (75)	1,000[b]	0.778
No	6 (30)	3 (25)		(0.154-3.927)
Genetics, n (%)				
Yes	30 (26.8)	7 (6.2)	<0.001[a]	5,488
No	82 (73.2)	105 (93.8)		(2,295-13,124)
Mosquito Coil, n (%)				
Yes	59 (52.7)	66 (58.9)	0.346[a]	0.776
No	53 (47.3)	46 (41.1)		(0.457-1.316)
Chalk, n (%)				
Yes	8 (7.1)	4 (3.6)	0.235[a]	2,077
No	104 (92.9)	108 (96.4)		(0.607-7.106)
Pesticides, n (%)				
Yes	14 (12.5)	10 (8.9)	0.388[a]	1,457
No	98 (87.5)	102 (91.1)		(0.618-3.435)
Waste Burning, n (%)				
Yes	6 (5.4)	2 (1.8)	0.280[b]	3,113
No	106 (94.6)	110 (98.2)		(0.615-15.769)
Firewood, n (%)				
Yes	29 (25.9)	10 (8.9)	0.001[a]	3,564
No	83 (74.1)	102 (91.1)		(1,642-7,735)
Air Pollution, n (%)				
Yes	8 (7.1)	2 (1.8)	0.052[a]	4,231
No	104 (92.9)	110 (98.2)		(0.878-20.387)

[a]Chi Square, Fischer's Exact

Multivariate analysis was used in this study to determine which independent variables have the most dominant influence in predicting the incidence of lung cancer in non-smoker women. The type of multivariate analysis used is multiple logistic regression because the dependent variable in this study is categorical. The variables included in the multivariate analysis are independent variables that have a p-value <0.25 from the results of the bivariate analysis. The eligible independent variables are age, passive smokers, tobacco exposure at home, genetic factors, limes, firewood, and air pollution.

By using the enter method and removing one by one the independent variables starting from the variable with the highest p-value> 0.05, then in the selection stage IV it was obtained that five independent variables significantly influenced the incidence of lung cancer in non-smoking women in this study, namely age (p = 0.008), passive smokers (p = 0.043), genetic factors (p < 0.001), exposure to firewood (p = 0.007), and air pollution factors (p = 0.041).

Based on the frequency distribution of age in this study, the average age in the case group was 57.86 years with the youngest age of 24 years and the oldest age of 87 years. Meanwhile, the control group with an average age of 47.4 years with the youngest age of 18 years and the oldest age of 86 years. The largest age group in the two study groups was aged ≥ 40 years, totaling 107 people (95.5%) in the case group and 82 people (73.2%) in the control group. In the case group, there were 107 people (95.5%) aged ≥ 40 years while in the control group subjects aged ≥ 40 years were 82 people (73.2%). Using the Chi-Square test showed that there was a significant relationship between age and the incidence of lung cancer in women who were not smokers (p <0.001). This is in line with research conducted by Kim et al. in Korea reporting the number of women who were not smokers who experienced lung cancer at the age of 55 to 79 years [8]. The research is also by a large study conducted by Wakele in 2007, namely that the incidence rate of lung cancer in women who never smoked aged 40 to 79 years ranged from 14 to 21 cases per 100,000 people per year [9].

Entamoeba spp. infection in human is commonly transmitted in areas with poor sanitation which allows contamination of drinking water and food with feces, with estimated prevalence range from 1% to 40% of the population in Central and South America, Africa, and Asia. In this study, we did not find any *Entamoeba* spp. in the samples. This may be due to the method used, because microscopic examination sensitivity for *Entamoeba* spp. detection varied from 10 to 50%, depending on the examiner's experience [12, 13].

Cryptosporidium spp. is an enteric protozoa found in both humans and livestock. Waterborne transmission for *Cryptosporidium* spp. has been reported via both surface water and groundwater [9, 14]. In this study, we also did not find any presence of *Cryptosporidium* spp. oocyst, probably due to the same

reason for the negative findings on *Entamoeba* spp. Additionally, we only performed simple direct examination, without further stainings such as Giemsa stain or acid-fast Ziehl-Neelsen to increase the sensitivity, due to budget limitation.

Giardia spp. is one of the most prevalent intestinal protozoan flagellate of the human. The transmission of *Giardia* spp. occurs either by direct contact with the feces of infected mammals or by contaminated food and water. Although there were local small farms in the area, we did not find any *Giardia* spp. in the collected samples nearby. This is probably due the similar reason mentioned for detection of *Entamoeba* spp. and *Cryptosporidium* spp. The collection of water sample was only done once for each, and probably the presence of those parasites was low below the detection sensitivity level of simple microscopic examination [15]. We did not employ any specific antigen detection methods such as direct fluorescent antibody tests, ELISA, or other immunochromatographic assays to diagnose these parasites in this study.

In this study, the most common finding we obtained was the presence of *Paramecium caudatum.* This ciliated protist was found is water source samples from open wells and nearby river streams. *Paramecium caudatum* is ubiquitous in fresh and brackish water, usually in the sludge of organic matters or the sewage area. *Paramecia* feed on microorganisms like bacteria, algae, and yeasts, and they play an important role in wastewater biological purification processes [16, 17]. The presence of *Paramecium caudatum* indicated that the water source was full with sludge of organic matters and possible presence of abundant coliform bacteria, which may not be that clean or safe for daily use.

Interestingly, we also found one sample from tap/piped water contaminated with hookworm larva. Hookworm is nematode parasite commonly transmitted through infested soil. It may cause chronic gastrointestinal tract infection, sucking the host's blood which leads to iron deficiency anemia. Zoonotic hookworm larva can also produce cutaneous larva migrans. Hookworm larva usually contaminates soil [18]. This finding indicates that the piped water distribution system was likely leaked and under poor maintenance, exposing contact to the surrounding contaminated soil. The proper and regular maintenance of the water distribution, including the distributing pipe maintenance, is essential to ensure the quality of the delivered safe water.

Although the time of the study was considered dated, but the significance of the message derived from this is still quite relevant. Recent massive sewage drainage excavation, an on-going project in the whole Medan city, is a changing environment which may pose threat to the safe water distribution system by introduction of contaminants to pollute the water. The risk for broken pipes during excavation, and the exposure of the water to the excavation's dumps, may expose risks to safe water delivery system maintenance for the city's households.

4. Discussion

In this study, we found that most of the study subjects had cell types based on cytology / histopathology were adenocarcinoma. Adenocarcinoma seems to be more common in non-smokers, but squamous cell types or other histology types are more common in heavy smokers and still smokers [9]. However, recently many researchers have stated that the most common histology type of lung cancer is adenocarcinoma [10]. This is in line with previous studies showing that people who have never smoked tend to have adenocarcinoma cancer [11, 12].

In this research, the majority of patients were in advanced stages, namely stage IV as many as 108 subjects, and stage III as many as four subjects. This is in line with the research of Santoro et al. which stated that the majority of research subjects who had lung cancer were in advanced stages and found that women were more likely than men to be diagnosed with lung cancer in more advanced stages [12].

In the case group, there were thirty people who had genetic factors for cancer, while in the control group, there were seven subjects who had genetic factors for cancer. Using the Chi-Square test, it was shown that there was a significant relationship between genetic factors and the incidence of lung cancer in women who were not smokers. This is in line with the research of Lee et al. in an epidemiological study showing that lung cancer patients who had never smoked and had a first-degree family history of cancer had an increased risk of lung cancer in individuals by a half compared to those who did not have a family history of cancer [13].

Genetic factors are the second dominant variable influencing the occurrence of lung cancer in women who do not smoke with the largest meaning that subjects who have genetic factors will be at risk of developing lung cancer 5.611 times greater than subjects who do not have genetic factors. This is following the research of Ernawati et al. on the risk factors for lung cancer in women treated in the West Sumatra Hospital Center in 2019, namely finding that women who have a history of cancer in the family are at 4.29 times greater risk of developing lung cancer [14].

In the case group, there were higher percentage passive smokers than in the control group, using the Chi-Square test showed that there was a significant relationship between passive smokers and the incidence of lung cancer in women who were not smokers. Passive smoking has been established as a major risk factor among non-smokers [9]. Hackshaw et al. reported that for non-smokers who live with smokers, there is an increase in the risk of cancer compared to those who do not live with smokers [15]. Passive smokers tend to smoke more than smokers themselves, including mainstream and sidestream smoke which have a synergistic effect on the development of lung cancer [16].

Passive smoking is the fifth variable that influences the occurrence of lung cancer in women who do not smoke meaning that subjects who are passive smokers will be at risk of experiencing lung cancer 1.992 times greater than subjects who are not passive smokers. This is in line with research conducted in a prospective population-based study of 28,414-lifetime never-smokers in Japan, the hazard ratio for lung cancer incidence in women living with a smoking husband was 1.34% [9]. This research is also in line with research conducted by a study in Japan, reporting from 11 case-control studies that women who did not smoke and were exposed to their husband's cigarette smoke had a 1.28 times greater risk of developing lung cancer compared to women who were not exposed [17].

In the case group, there were higher percentage exposed to firewood while in the control group, ten subjects were exposed to firewood. Using the Chi-Square test, it was shown that there was a significant relationship between exposure to firewood and the incidence of lung cancer in non-smoking women. Various studies have shown that prolonged inhalation of cooking smoke and high-temperature oil in poorly ventilated rooms is the cause of high rates of lung cancer in non-smoking women in China and Taiwan [18-20].

Indoor burning of coal and biomass in poorly ventilated areas for heating and cooking has also been associated with the development of lung cancer in non-smoking women in low-income countries [21]. Household smoke exposure, namely exposure to firewood, is the fourth variable that influences the occurrence of lung cancer in non-smoking women, meaning that subjects exposed to firewood will be at risk of developing lung cancer 3.157 times greater than subjects not exposed to firewood. This study is in line with Bruce et al.'s research in 2015 reporting the risk of lung cancer in the use of firewood for cooking 1.15 times and for heating 1.17 times [22].

Air pollution factor is the most dominant variable influencing the occurrence of lung cancer in women who do not smoke meaning that subjects exposed to air pollution will be at risk of developing lung cancer 5.817 times greater than subjects who are not exposed to air pollution. This is almost the same as several studies that have reported an increased risk of cancer as a result of exposure to certain air pollution components. Furthermore, it is estimated that 1-3.6% of lung cancers in Europe may be related to atmospheric pollution as much as 5-7% in the category of never smokers [23].

5. Conclussion

In this research, it is estimated that age above 40, passive smokers, exposure to firewood, and genetics are the risk factors that significantly influence the occurrence of lung cancer in non-smoking women.

6. Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available due to privacy and ethical considerations but are available from the corresponding author upon reasonable request.

7. Ethical Statement

Sumatera Medical Journal (SUMEJ) is a peer-reviewed electronic international journal. This statement below clarifies ethical behavior of all parties involved in the act of publishing an article in Sumatera Medical Journal (SUMEJ), including the authors, the chief editor, the Editorial Board, the peer-reviewer and the publisher (TALENTA Publisher Universitas Sumatera Utara). This statement is based on COPE’s Best Practice Guidelines for Journal Editors

8. Authors Contributions

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11. Conflict of Interest
Authors declares no conflict of interest.

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