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Review Article

Screening approach and early detection of lung cancer in non-smoking female

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Abstract

The prevalence of lung cancer is generally dominant in men as cancer with the highest mortality rate. However, the mortality rate for lung cancer in women has increased, which placed lung cancer as the first deadliest cancer based on mortality rate followed by breast cancer. In Indonesia, lung cancer ranks third in the incidence of lung cancer in both gender and ranks first in the incidence in men. For women, lung cancer is not in the top 5 of the highest cancer's incidence. There are several risk factors in women, such as passive smoking, exposure to pesticides, exposure to biomass, and others. Exposure to biomass includes exposure to wood smoke, mosquito coils, and lime dust. Therefore, early detection of those who have been exposed to the above risk factors is needed. Two components of cancer detection include early detection and screening. Early detection focuses on detecting symptomatic patients as early as possible, whereas screening consists of screening healthy individuals to identify those with cancer before symptoms appear. A global study by The National Lung Screening Trial (NLST) showed a 20% reduction in mortality from lung cancer by screening using Low Dose CT-Scan (LDCT), thus making LDCT the modality of choice for screening lung cancer patients.

Keywords: *early detection*, *female, lung cancer*, *non-smokers*, *screening*

Abstrak

Prevalensi kanker paru pada umumnya dominan pada laki-laki dengan angka kematian tertinggi namun angka kematian kanker paru pada perempuan mengalami peningkatan sehingga menjadikan kanker paru menjadi angka kematian tertinggi diikuti kanker payudara untuk perempuan. Di Indonesia, kanker paru menduduki urutan ketiga untuk insidens kanker paru secara umum, dan pertama untuk insidens pada laki-laki. Untuk perempuan sendiri, kanker paru memang belum menduduki 5 besar angka kejadian tertinggi kanker. Terdapat beberapa faktor risiko terkait kanker paru pada perempuan yaitu perokok pasif, paparan pestisida, paparan biomassa, dan lainnya. Paparan biomassa termasuk didalamnya paparan asap kayu, obat nyamuk bakar, dan debu kapur. Sehingga untuk itu, diperlukan deteksi dini pada orang-orang yang terpapar faktor risiko di atas. Dua komponen deteksi kanker adalah deteksi dini dan skrining. Deteksi dini berfokus mendeteksi pasien bergejala sedini mungkin, sedangkan skrining terdiri atas pemeriksaan individu yang sehat untuk mengidentifikasi mereka yang menderita kanker sebelum gejala muncul. Studi global oleh *The National Lung Screening Trial* (NLST) menunjukkan penurunan 20% angka kematian akibat kanker paru dengan skrining menggunakan *Low Dose CT-Scan* (LDCT) sehingga LDCT menjadi modalitas pilihan untuk skrining pasien kanker paru.

Kata kunci*: deteksi dini, female, kanker paru, non-smokers, skrining*

This article is translated from the author's professorial inauguration speech on March the 12th 2022 atAuditorium Universitas Sumatera Utara, Medan

Background

Globally, lung cancer cases have significantly increased in recent years. The prevalence of lung cancer is generally dominant in men with the highest mortality rate amongst all types of cancer.[1,2] At the same time, women's mortality rate from lung cancer continues to increase. There were 62,590 deaths per year for women and 135,360 deaths for both sexes. According to the data, lung cancer in women reaches 13% of all cancer cases and a 21% mortality rate compared to the total number of cancer cases.[1–3] In Indonesia, lung cancer ranks third in the incidence of lung cancer in general, and first in terms of the incidence in men. For women, lung cancer is not yet in the top five of the highest incidence of cancer.[4]

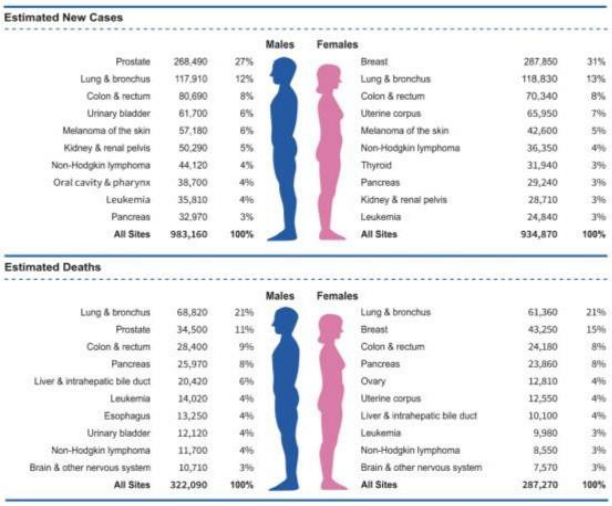

Figure 1. The estimated incidence of new cases and mortality rates in the top 10 highest cancers by gender in 2022 globally and the United States.[3]

By 2030, lung cancer in women is expected to increase by 43% in 52 countries with the median age-standardized mortality rate for lung cancer increasing from 11.2 to 16 per 100,000 deaths, which exceeds the observed Age-standardized Mortality Rate (ASMR) for breast cancer.[5] This happened due to several factors, including the increasing prevalence of smoking among adolescent girls from low-income and middle-income countries in Africa, South America, and the Middle East which is statistically higher than in high-incomecountries.[6] However, this incidence is also increasing in non-smokers and young women worldwide. In addition, only 50% of lungcancers in women are associated with tobacco smoke. Jemal et al. reported that the increased incidence of lung cancer in young women in the US was not fully explained by smoking patterns.[7] Other factors such as high air pollution, individual genetic susceptibility, and occupational exposure also contribute to the development of lung cancer in women.[8]

Summary statistic 2020			
	Males	**Females**	**Both sexes**
Population	137 717 861	135 805 760	273 523 621
Number of new cancer cases	183 368	213 546	396 914
Age-standardized incidence rate (World)	138.9	145.4	141.1
Risk of developing cancer before the age of 75 years (%)	15.0	14.9	14.9
Number of cancer deaths	124 698	109 813	234 511
Age-standardized mortality rate (World)	96.3	75.9	85.1
Risk of dying from cancer before the age of 75 years (%)	10.5	8.3	9.4
5-year prevalent cases	389 640	556 448	946 088
Top 5 most frequent cancers excluding non-melanoma skin cancer (ranked by cases)	Lung Colorectum Liver Nasopharynx Prostate	Breast Cervix uteri Ovary Colorectum Thyroid	Breast Cervix uteri Lung Colorectum Liver

Figure 2. Cancer incidence rate for Indonesia[4]

Lung Cancer Characteristicsin Women

Histologically, there are 2 types of lung cancer, namely small cell lung cancer (SCLC) and non-small cell carcinoma(NSCLC). NSCLC is the type of lung cancer with the highest prevalence (85%). NSCLC itself consists of three subtypes: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Approximately 40%-60% of lung cancers in women are adenocarcinoma. Whereas, there are about 10-30% cases ofsquamous cell carcinoma from all lung cancers diagnosed.[9–11] Lung adenocarcinoma is a heterogeneous type of cancer and shows a lower association with smoking habits compared to other lung cancer subtypes. It is estimated that up to 50% of women with lung adenocarcinoma are non-smokers, compared with 10-15% of non-smoking men who suffer from this type of cancer.[12]

Clinical characteristics differ between women and men; such as women are diagnosed at an earlier age, women are more likely to be non-smokers, they show a less advanced stage at first diagnosis, and they have significantly better outcomes and survivalat all stages of lung cancer.[13] Hormonal status is rarely evaluated in studies. However, an independent study in pre-menopausal women showed worse clinical characteristics reflected in clinical manifestations at first diagnosis, namely advanced stage, poor histo-pathological differentiation, a higher number of metastases, and shorter overall survival compared to postmenopausal women and men. Estrogen hormone considered essential role in determining the poor outcomes in lung cancer females in productive age.[14-16]

Besides these poor clinical characteristics, it should also be noted that women with a diagnosis of non-small cell lung cancer have a different response to treatment. Women with lung cancer are more responsive to chemotherapy, especially platinum-based treatment and tyrosine kinase inhibitor (TKI) based therapy, but less responsive to immuno-therapy.[9,17–19] Women are more likely to be ERCC1-negative, a protein that plays a significant role in DNA repair. This explains the more significant benefit of chemotherapy in women than in men. Mutations in EGFR (exons 18-21) that are a requirement for targeted therapy are also more common in women and are associated with the expression of the estrogen receptor.[20,21]

Apart from the clinical point of view, a deeper study of lung cancer's pathogenesis showed some genetic mutations in lung cancer that are more common in women, and some genes are expressed differently according to gender. Cytochrome CYP1A1 which is known as one of the main enzymes in nicotine metabolism and also as the main substance in cigarette smoke is overexpressed in women.[22] Additionally, women also have a lower DNA repair capacity as well as an increase in the gastrin-releasing peptide receptor (GRPR) which stimulates cancer cell proliferation. Tobacco-associated p53 mutations are also more common in women.[20,21] All these data indicate that women are more susceptible to tobacco carcinogens than men.

Lung Cancer Risk Factors in Women

Tobacco cigarette remains an important factor associated with lung cancer in women because women have a higher susceptibility than men with the same amount of exposure.[23] Passive smoking is a relevant risk factor in non-smoking women, this is supported by research that shows 64% of deaths from lung cancer are associated with secondhand smoke in women. Passive smokers are exposed to two sources of carcinogens: smoke produced by burning cigarettes and cigarette smoke exhaled by smokers, where benzo-a-pyrene diol epoxide which is the main carcinogen of tobacco is found in both sources.[24]

Exposure to biomass is a risk factor that is always considered in the etiology of lung cancer in non-smoking women. Exposure to biomass includes exposure to wood smoke, mosquito coils, and lime dust. Exposure to wood smoke affects women, especially in developing countries, where wood is used for cooking and keeping homes warm. An estimated 34.4% of non-smoking patients diagnosed with lung cancer in Mexico are chronically exposed to wood smoke. Wood smoke exposure was also strongly associated with adenocarcinoma subtypes and higher EGFR mutations.[25] Among non-smokers diagnosed with lung cancer in China and India,smoke from cooking oil is an important riskfactor for lung cancer.[26] When cooking, the oil is brought to a high temperature and produces smoke that contains lung carcinogens, such as polycyclic aromatic hydrocarbons, which result in DNA oxidative damage and lipid peroxidation.[27] In addition, mosquito coils are a significant risk factor for lung cancer in women in tropical countries. The risk of lung cancer was significantly higher in individuals who used mosquito coils more than three days per week than in non-combustible mosquitorepellents such as electric or spray mosquito repellents. Recently, it was also found that there was an increase in the incidence of lung cancer in teachers who were exposed to lime dust for decades. Fine lime particles can cause oxidative damage to alveolar macrophages and result in cytotoxicity, hence it can act as a carcinogen that affects the incidence of lung cancer in the UK.[28,29]

One of the other highest risk factors for lung cancer is exposure to pesticides. A large number of studies have described the relationship between several classes ofinsecticides, herbicides, and contaminants of widely used herbicides and the incidence of lung cancer in nonsmokers.[30,31]

Ambient air pollution, especially particulate matter (PM 2.5), is also associated with a high risk of developing lung cancer because of the hydrocarbons and heavy metals in PM compounds carry carcinogenic potential. PM exposure results in inflammation associated with lung cancer.[32,33] Several reports have found that women exhibit a higher risk of air pollution than men may be due to higher susceptibility to carcinogens, reducedDNA repair capacity, and polymorphisms of xenobiotic-metabolizing genes in women.[34-36] Ambient air pollution remains a significant risk factor for lung cancer in non-smoking women who live in cities with high levels of air pollution.[34]

Currently, we have conducted research related to lung cancer in women. It was found that the majority of lung cancer patients were women aged over 50 years (76.2%), adenocarcinoma type (82.9%), stage IV (36.4%), with one biomass exposure such as lime dust (4.5%), pesticides (14.7%), firewood (10.2%),

mosquito coils (4.5%), and about 20.5% of patients were passive smokers. About 33% of the subjects were exposed to two sources of smoke with the majority being cigarette smoke and firewood.[37]

Lung Cancer Screening in Women

As stated above, it turns out that lung cancer is not only caused by cigarettes and exposure to smoke but several other factors that contribute to the occurrence of lung cancer. Therefore, early detection of people exposed to the above risk factors is needed. Two components of cancer detection include early detection and screening. Early detection focuses on detecting symptomatic patients as early as possible, whereas screening consists of screening healthy individuals to identify those with cancer before symptoms appear.[38]

Early detection is an action where examinations are carried out on those who are already symptomatic. Early detection is aprogram that aims to reduce the proportion of patients diagnosed at an advanced stage. Early detection has two main components:[38]

1. Increasing awareness of the first signs of cancer, both by doctors, nurses, and other health care providers and among the general public.
2. Increasing accessibility and affordability of diagnosis and treatment services, and increasing referrals from first-level health services/facilities to secondary andtertiary health facilities/services.

Whereby, ***screening*** is a simple examination in a healthy population to identify individuals who have the disease but do not show any symptoms yet. Screening programs should be carried out only when their effectiveness has been proven and the area has sufficient resources. Screening is often associated with unwanted effects, even when done correctly, for example:[38]

1. The results of a false-positive screening examination that require a gold standard examination (in the form of additional examinations, or invasive measures)
2. False-negative screening examination resulting in delayed presentation/diagnosis when symptoms appear, and
3. Excessive preclinical diagnosis/treatment of cancer that never causes symptoms or poses a serious health threat and involves unnecessary invasive treatment.

Most lung cancer patients are diagnosed with advanced stages and have shown severe symptoms. Thus, curative treatment is no longer an option. This means that effective screening modalities are required to reduce lung cancer mortality. Sputum cytology, chest radiography, and chest CT scan have been studied in various studies as potential screening modalities for lung cancer. A global study by The National Lung Screening Trial (NLST) showed a 20% reduction in mortality from lung cancer by screening using Low Dose CT-Scan (LDCT) thus making LDCT the modality of choice for screening lung cancer patients.[39]

The National Comprehensive Cancer Network (NCCN) and the American Association for Thoracic Surgery (AATS) recommend adults (50-74 years old), with additional risk factors for lung cancer, such asa history of other cancers or lung disease (COPD, diffuse pulmonary fibrosis and others), a family history of lung cancer, exposure to radon, and exposure to carcinogens at work should start screening at the age of 50.[40] For further details refer to Figure 3.

Figure 3. Lung cancer screening algorithm in at-risk populations based on NCCN 2018.[40]

The problem that is often found inLDCT is the high number of false positives. Based on the NLST, a positive result for lung cancer is shown if nodules with a diameter of 4mm were found. In contrast to using the NELSON screening, which is based on nodule volume, i.e. nodules <50 mm^3 (4.6 mm in diameter) are negative, nodules >500 mm^3 (diameter >9.8mm) are positive, and nodules between 50 and 500 mm^3 are undefined. Undefined nodules require re-evaluation after three months using low dose CT to assess growth,and doubling times of nodule volume.[41] NCCNitself divides LDCT findings into three categories based on the appearance of the nodules, namely solid nodules, subsolid nodules, and nonsolid nodules. For each category, it will be further divided based on its size to determine the next action to be taken.[40]

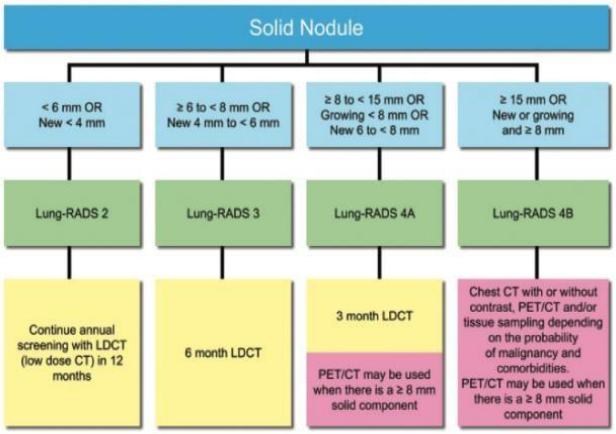

Figure 4. Management of solid lung nodules detected at screening[40,42,43]

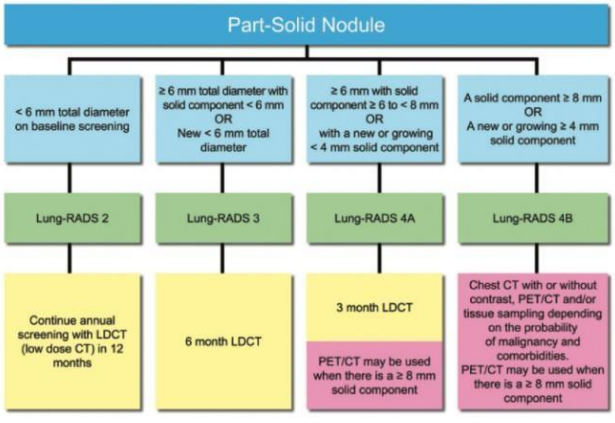

Figure 5. Management of partially solid lungnodules detected at screening[40,42,43]

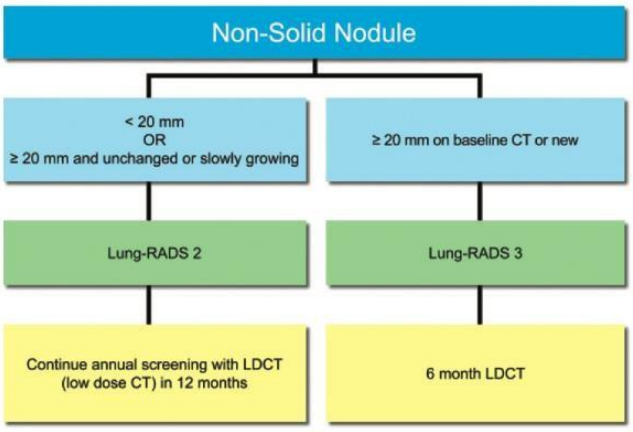

Figure 6. Management of non-solid lungnodules detected at screening[40,42,43]

Challenges Related to the Importance of Screening and Early Detection of Lung Cancer in Women

Various studies and guidelines have been described in every section above. Lung cancer in women is still an interesting topic,but unfortunately, it has not been widelysocialized in the community. Screening and early detection of lung cancer in women still poses many challenges for clinicians.

The first challenge is educating the public about the incidence of lung cancer in women. Currently, most of our society still thinks that lung cancer is only caused by smoking. Hence, the population at risk is active smokers. For this reason, women with respiratory symptoms such as shortness of breath, chest pain, cough, coughing up blood, and weight loss are more often associated with pulmonary infections, especially tuberculosis. As a result, many delays in diagnosis occur, especially in developing countries. In addition, public awareness for a regular check-up with doctors amongst at-risk populations is still a concern. Our society still postponed to go for a check-up to the hospital if they do not have serious complaints. Futhermore, most of the new patients would only go for a check-up after taking over-the-counter drugs and did not experience a significant improvement insymptoms.

The second challenge is in terms of diagnosis. Despite having risk factors for radiation exposure, thoracic LDCTexamination is still the best choice for early detection of lung cancer. Unfortunately, there is still an issue with a universal insurance claim, i.e.

Social Security Administrator for Health (*Badan Penyelenggara Jaminan Sosial/BPJS Kesehatan*) which is the largest insurance company in Indonesia. The act of early detection without clinical manifestations is still a debate, especially for high-cost examinations such as Chest CT-Scan. Therefore, it is necessary to have a comprehensive discussion between policymakers and clinicians to socialize early detection aiming to reduce mortality in lungcancer, especially in the female population

Conclusion

1. Currently, there is an increase in lung cancer cases in women with the highest mortality rate for all types of cancer.
2. In addition to a cultural shift where there is an increase in smoking rates among women, exposure to cigarette smoke isthe most common cause of lung cancer inwomen, followed by other factors such as exposure to biomass and air pollution.
3. For exposure to the same risk factors, pre-menopausal women are more likely to develop lung cancer with more advanced stages and worse clinical characteristics than men or post-menopausal women. It is suspected that hormonal factors suchas estrogen play a huge role in the incidence of lung cancer.
4. Screening and early detection of lung cancer are needed to reduce the mortality rate from lung cancer. Early detection focuses on detecting symptomatic patients as early as possible, whereas screening consists of screening healthy individuals to identify those with cancer before symptoms appear.
5. In patients with high-risk factors, low dose CT-Scan is the best modality for early detection of lung cancer and can significantly reduce lung cancer mortality rate by up to 20%.
6. There are several challenges in the early detection and screening of female patients with high-risk factors for lung cancer, including the low awareness ofthe community for a check-up and the thoracic LDCT examination is not coveredby the national insurance.

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