Acta Scientific Women's Health (ISSN: 2582-3205)

Volume 4 Issue 7 July 2022

Mini Review

Lung Cancer in Asian Women

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DOI: 10.31080/ASWH.2022.04.0390

Received: May 25, 2022

Published: June 16, 2022

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Abstract

Lung cancer is an aggressive and heterogeneous disease. A global epidemic of lung cancer in women is sweeping the globe. Although cigarette smoking is the leading cause of lung cancer in both women and men, several studies have found significant gender differences. Lung cancer is becoming more common among nonsmokers, particularly Asian women. This mini review summarizes the epidemic of lung cancer in Asian women and the importance of screening with the use of low-dose CT for early detection and thus reduce lung cancer mortality rate.

Keywords: Lung cancer, women, non-smoker, screening, Low-dose CT

Epidemiology and current trends

Worldwide, lung cancer remains the leading cause of cancer mortality in women and men. In Asian women, the incidence of lung cancer is surpassed only by breast and colon cancer with an estimated 423 238 new cases in 2020 (9.4%). Lung cancer is the second most common cause of cancer mortality in Asian women with 1% difference compared to breast cancer (15%) [1]. Adenocarcinoma, the most frequent type of lung cancer in women, has been gradually increasing in a number of countries around the world [2].

The human development index (HDI) showed a trend in lung cancer incidence, with the incidence of lung cancer being highest in regions with a very high HDI and lowest in countries with a low HDI [3]. Lung cancer is also becoming more common when people's socioeconomic status declines [4]. According to a global survey undertaken by the Chinese University of Hong Kong and the Association of Pacific Rim Universities, East Asia topped the world's incidence and death of lung cancer in 2020. Between 2015 and 2030, the median age-standardized mortality rates (ASMR) for lung cancer is likely to rise from 11.2 to 16.0 in 52 countries, while breast cancer is expected to fall from 16.0 to 14.7. In half of the countries surveyed, whereby 75% of those classified as high-income countries, the ASMR for lung cancer has already surpassed or will surpass the ASMR for breast cancer by 2030 [5]. In Asia, more than half of all lung cancer patients are never smokers. Although the cause of the high risk of lung cancer among Asian never-smokers is unknown, vapours from cooking oils and coal burning in poorly ventilated settings have been suggested [6]. In never-smokers, adenocarcinoma is the most common lung cancer histology, with distinct cancer driver mutations [7].

Lung cancer screening

The American National Lung Screening Trial found that screening with low-dose computed tomography (LDCT) reduced lung cancer mortality in high-risk individuals by 20% when compared to chest radiography, which detected a higher proportion of lung cancer at stage I or II. [9]. On the other hand, separate analyses by gender, found that women who received LDCT had significantly lower lung cancer mortality [10]. To corroborate, six Chinese hospitals

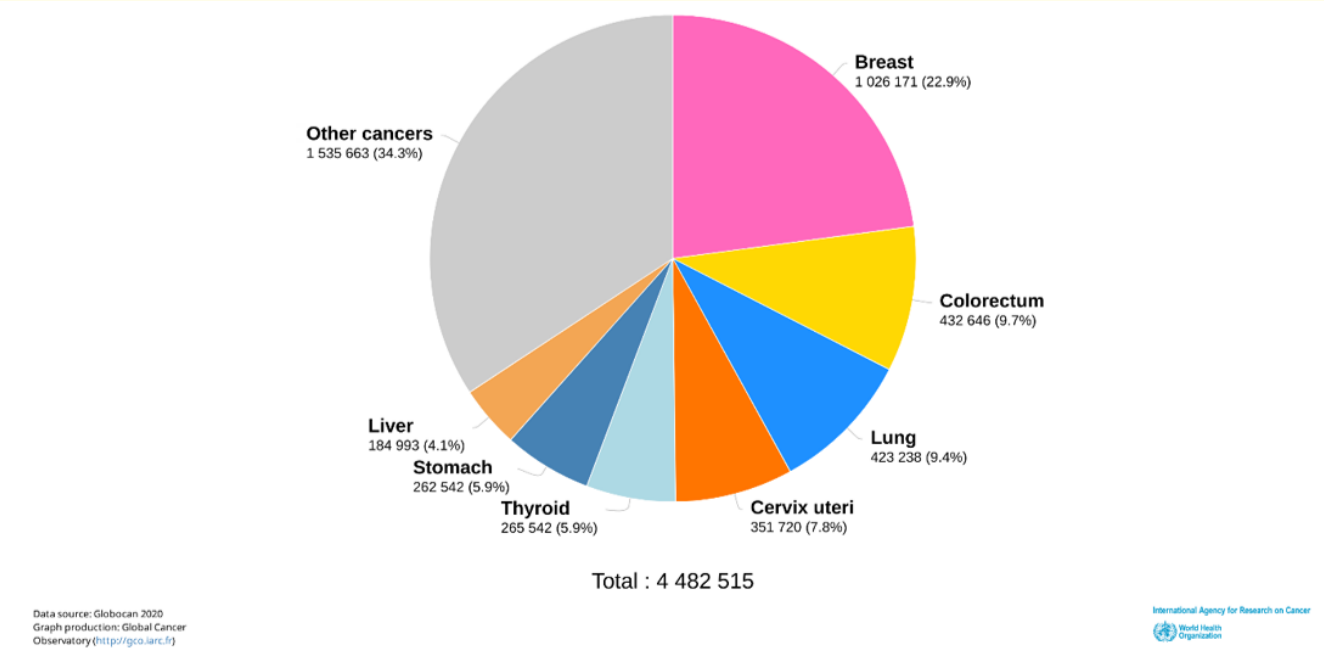

Figure 1: Estimated number of cancer cases by type in 2020 in Asian women (GLOBOCAN 2020 [8]).

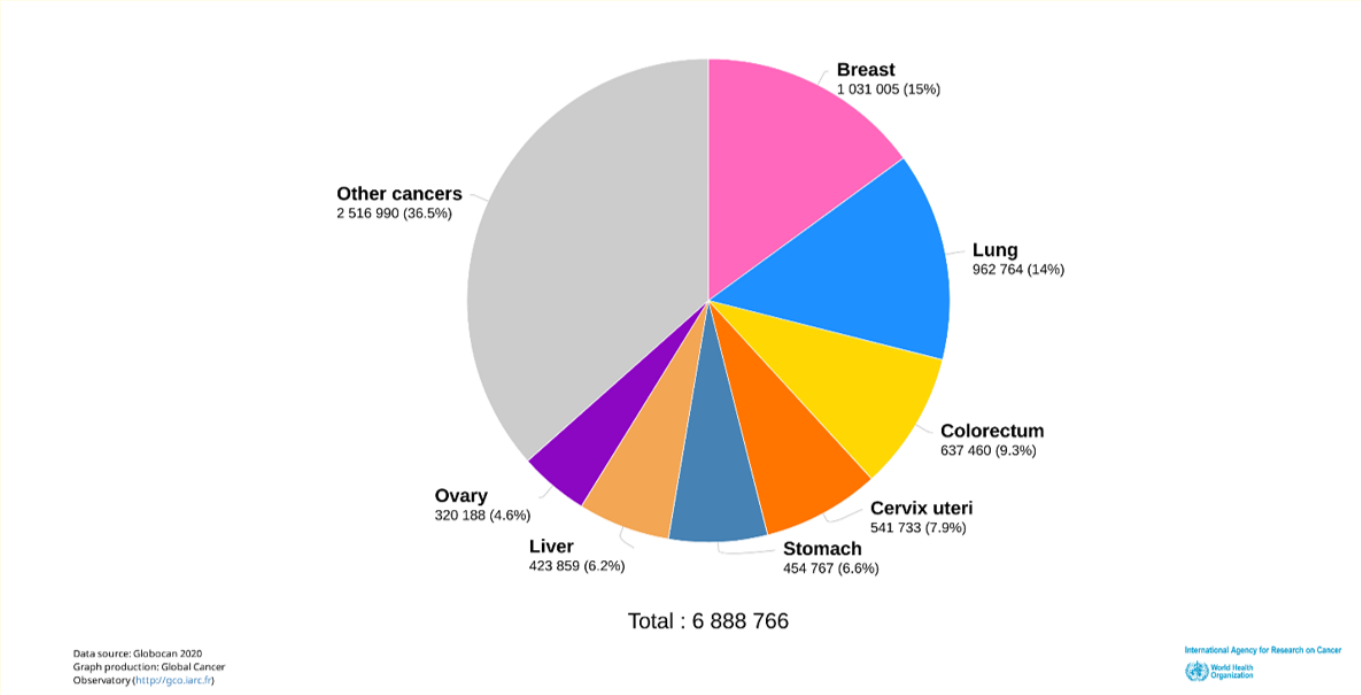

Figure 2: Estimated number of cancer deaths in 2020 among Asian women (GLOBOCAN 2020 [8]).

have added LDCT screening to their staff' routine health checks, detecting more lung cancers in nonsmokers than smokers and in women than men, concluding that the vast majority of patients have a good prognosis [11]. Furthermore, the "Initiative for European Lung Screening" by a large international association of doctors and other healthcare professionals recommended the urgent need to implement lung cancer screening with LDCT in Europe in order for early stage diagnosis of lung cancer and reduce mortality rates [12].

Because there is no evidence that chest radiography and sputum cytology tests, either alone or in combination, reduce lung cancer mortality, they are not recommended for lung cancer screening. Despite the fact that blood and serum-based biomarkers are promising adjuncts to LDCT for lung cancer screening, there is currently no high-quality evidence to support or guide their use in clinical practice [13].

Lung cancer risk factors in women

Lung cancer is known to be caused by a number of factors, including increased smoking rates, occupational exposure to toxins, poor diet, and unequal health care access in many regions of the world [14]. Women are more likely than men to acquire lung cancer as a result of smoking [15]. Overall, women had nearly three times the risk of lung cancer as men and had higher DNA adduct levels than men. Also compared to men, women had more mutations in the tumor suppressor gene p53 and the proto-oncogene K-RAS [16]. The combination of cigarette carcinogens with endogenous and exogenous sex hormones is a growing significant risk in the development of lung cancer. Furthermore, lung cancer is more common in women who use hormone replacement treatment or oral contraceptives [17].

Although research into sex-based differences in lung cancer biology, natural history, and therapeutic response has been promising, more work is needed to better understand the impact of these characteristics in order to design future lung cancer therapy and screening trials.

Lung cancer types and Molecular profiles

Lung carcinomas are classified based on their size and appearance. The two main types of lung cancer are the Small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC) [18]. NSCLC is the most common type, accounting for 85% of all cases. The histologic subtypes of NSCLC include squamous cell carcinoma or big cell carcinoma, which originates from epithelial cells lining the bronchi, and adenocarcinoma, which develops from gland tissue in the peripheral portions of the lung. Adenocarcinoma is more prevalent in women than squamous cell carcinoma or large-cell lung cancer. Squamous cell carcinoma, on the other hand, is the most prevalent subtype of lung cancer in men [16]. Lung cancer driver genes have been found in lung cancer in never-smokers.

Biomarker testing can identify patient subgroups that are more likely to benefit from a treatment. This indicator is critical for doctors to understand the complexities of treatment choices. In NSCLC, a number of biomarkers are being examined in routine diagnostics, including EGFR and BRAF mutations, as well as ALK and ROS1 rearrangements and PD-L1 expression. Asian American patients were more likely to be never smokers and have an EGFR mutation compared to Caucasians who are more likely having KRAS mutation [7].

Next-generation sequencing (NGS) techniques for oncogenic driver genomic profiling have improved the gathering of genetic data with clinical utility. Furthermore, this application is now available for liquid biopsies, such as plasma, urine, and cerebrospinal fluids, in addition to tumour tissue analysis. The availability of targeted sequencing panels that cover genetic alterations in hundreds of genes allows for entire genomic profiling of each patient's tumour to be done with just one experiment. Thus, all metastatic NSCLC patients should be offered thorough genetic sequencing in order to improve the use of precision-personalized medicine in this scenario and provide more therapeutic options. Importantly, additional genetic profiles of lung malignancies have been discovered using NGS.

When a tissue diagnosis isn't possible, serum biomarkers including neuron-specific enolase, progastrin-releasing peptide, carcinoembryonic antigen, cytokeratin 19 CYFRA 21-1, and squamous cell carcinoma antigen may help with lung cancer differential diagnosis [19].

Treatment

The type and stage of cancer, as well as other characteristics, influence therapeutic decisions. Surgery, radiation therapy, chemotherapy, and targeted therapy are all options for lung

cancer treatment [20]. The availability of predictive biomarkers for molecularly targeted therapeutics and immune checkpoint inhibitors (Table 1) have changed the management of NSCLC, particularly the adenocarcinoma subtype [21], in the recent decade. Testing for sensitizing mutations in the EGFR is currently required for patients with advanced adenocarcinomas before receiving anti-EGFR medicines such erlotinib, gefitinib, afatinib, or osimertinib [22]. Patients who are unable to furnish tumor samples may have their plasma tested for EGFR mutations. Testing for ALK and ROS1 gene rearrangement is required to predict crizotinib response [23]. Treatment with ceritinib, alectinib, or brigatinib is also contingent on the existence of ALK rearrangements [24]. Meanwhile, in the first-line therapy of patients with advanced adenocarcinoma or squamous cell NSCLCs, PD-L1 should be assessed using an approved assay to predict response to the single immunotherapy with pembrolizumab [25]. However, the availability and affordability of the immunotherapy options for lung cancer treatment is limited.

Table 1: List of FDA approved molecular targeted therapy and immune checkpoint inhibitors for NSCLC.

Oncogenic driver mutations	
EGFR mutation positive	Erlotinib, Afatinib, Osimertinib, Gefitinib, Dacomitinib
ALK rearrangement positive	Ceritinib, Crizotinib, Alectinib, Brigatinib
ROS1 rearrangement positive	Crizotinib, Ceritinib, Entrectinib,
BRAF V600E mutation positive	Dabrafenib/Trametinib
MET Exon 14 Skipping mutation	Crizotinib, Capmatinib,
NTRK Gene fusion positive	Larotrectinib, Entrectinib
RET Rearrangement positive	Selpercatinib/LOXO-292, Cabozantinib, Vandetanib
KRAS	ICIs, nivolumab
Immune checkpoint inhibitors	
Programmed cell death 1 (PD-1)/ programmed cell death ligand 1 (PD-L1)	Pembrolizumab, Atezolizumab, Nivolumab + Ipilimumab
Cytotoxic T-lymphocyte antigen 4 (CTLA4)	Ipilimumab, Tremelimumab

Conclusion

Lung cancer accounts for about 1.8 million deaths worldwide and is the leading cause of cancer deaths in women in 28 countries. Never-smoking patients account for 15% of lung cancer patients, more often women and adenocarcinoma. The increased incidence of lung cancer in women never-smokers despite less exposure to occupational carcinogens lending weight to other mechanisms driving the increased incidence in women. Effective screening program showed an increased early-stage incidence, suggesting that screening detects cancer early, and a decreased late-stage incidence, demonstrating that screening reduces the presentation of advanced disease. LDCT detected more *in situ* and stage I lung cancers. Therefore, we highlight the urgent need to widely implement effective screening program for lung cancer using LDCT among non-smoking women in Asia.

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