Editorial

eISSN 2005-8330
https://doi.org/10.3348/kjr.2022.0190
Korean J Radiol 2022;23(6):571-573

Korean Journal of Radiology
KJR

Potential Overdiagnosis with CT Lung Cancer Screening in Taiwanese Female: Status in South Korea

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Take-home points

- Lung cancer in never-smokers, especially in female, is a major concern in East Asia.
- Lung cancer statistics in South Korea and Taiwan show a marked increase in early-stage disease, with relatively stable late-stage disease in female during the last decade, suggesting potential overdiagnosis with low-dose CT lung cancer screening.
- Widespread CT lung cancer screening is not recommended in never-smokers unless new evidence suggests its utility in identifying high-risk individuals in this subpopulation.

Lung cancer is the leading cause of cancer-related deaths, representing one in five (18.0%) deaths worldwide as of 2020 [1]. As approximately two-thirds of lung cancer-related deaths are attributable to smoking, effective tobacco control may reduce these numbers. Several randomized controlled clinical trials have demonstrated the efficacy of low-dose CT (LDCT) screening in reducing lung cancer mortality. Based on these results, a national lung cancer screening program was initiated in Korea in 2019 after a 2-year feasibility study known as the Korean Lung Cancer Screening Project [2]. This national screening program targets high-risk populations aged 55–74 years with a smoking history of at least 30 pack-years.

The proportion of lung cancer in never-smokers is expected to increase with decreasing smoking rates and the successful implementation of smoking prevention and cessation programs. In addition, lung cancers in never-smokers and smokers show sex-related, pathological, and molecular differences. A high proportion of East Asian never-smoker female are diagnosed with lung cancer, more commonly adenocarcinomas, with strikingly different mutation patterns. Non-smoking status is also a strong clinical predictor in patients who would benefit from treatment with epidermal growth factor receptor tyrosine kinase inhibitors. Therefore, lung cancer in never-smokers, especially female, is a major public health concern in East Asia.

Opportunistic LDCT lung cancer screening has been popularized in East Asia, and several observational studies have compared lung cancers detected in never-smokers and smokers in Korea, Japan, and China [3-5]. In these studies, 28%–93% of lung cancers were found in never-smokers in the study population, and more than 93% of lung cancers in never-smokers were stage 0 or I. The detection rate of lung cancers in never-smokers (0.45%–2.22%) was comparable to that in smokers (0.86%–1.36%). Based on these results, some study groups have suggested that lung cancer screening should be performed routinely in never-smokers [3,4].

Gao et al. [6] recently published a study on the

Received: March 21, 2022 **Accepted:** March 27, 2022
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association between CT screening promotion and lung cancer overdiagnosis in Taiwanese female. Their population-based ecological cohort study using lung cancer statistics from the Taiwan Cancer Registry from January 2004 to December 2018 aimed to determine the association between lung cancer incidence and promotion of LDCT screening among Taiwanese famele with a smoking prevalence of less than 5%. Between 2004 and 2018, the incidence of early stage (stages 0–I) lung cancer increased more than 6-fold (from 2.3 to 14.4 per 100000 female). During the same period, the incidence of late-stage (stages II–IV) lung cancer remained unchanged (from 18.7 to 19.3 per 100000 female). This increase in early stage incidence without a concomitant decline in late-stage incidence strongly suggests overdiagnosis. Although the 5-year survival after lung cancer in female more than doubled (from 18% in 2004 to 40% in 2013), lung cancer mortality decreased only slightly (from 17 to 16 per 100000 population).

As similar trends are expected in other East Asian countries, we reviewed the lung cancer statistics in South Korea using the Korea National Cancer Incidence Database. From 1999 to 2019, the number of new lung cancer cases increased 2.1 fold (from 9744 to 20331) in male and 2.8-fold (from 3485 to 9629) in female. Lung cancer deaths also increased by 1.8-fold (from 7779 to 13698) in male and by 1.8-fold (from 2656 to 4876) in female. The increase in both crude incidence per 100000 (from 41.1 to 79.4 in male and from 14.8 to 37.4 in female) and mortality per 100000 (from 32.9 to 53.5 in male and from 11.3 to 19.0 in female) is closely related to an increase in the aged population. During the same period, the age-standardized incidence per 100000 population decreased by 19% (from 51.4 to 41.7) in male. Age-standardized mortality per 100000 population also decreased by 35% (from 41.7 to 27.1) in male and 26% (from 9.5 to 7.0) in female. However, the age-standardized incidence per 100000 increased by 35% (from 12.5 to 16.9) in female (Fig. 1). The decrease in the incidence of lung cancer in male may be related to a decreased smoking rate. From 1998 to 2018, the current smoking rate decreased (from 66.3% to 36.7%) in male and remained stable (from 6.6% to 7.5%) in female. From 2006 to 2019, age-standardized incidence per 100000 of early-stage (localized stage) lung cancer increased by 15% (from 8.4 to 9.7) in male and 128% (from 2.7 to 9.1) in female, while that of late-stage (regional and distant stages) lung cancer remained unchanged (from 28.5 to 28.4) in male and increased by 24% (from 7.8 to 9.7) in female (Fig. 2).

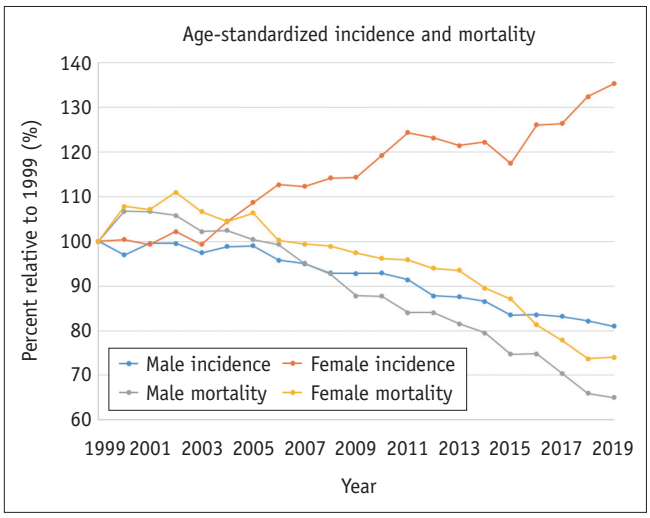

Fig. 1. Lung cancer incidence and mortality in Korean male and female (1999–2019).

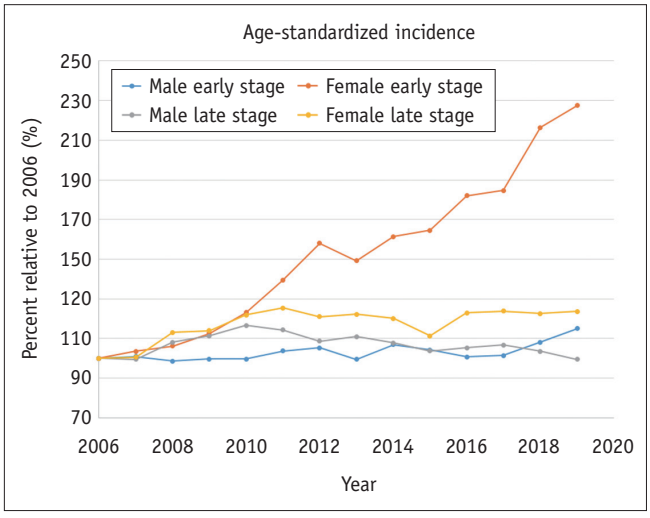

Fig. 2. Stage-specific lung cancer incidence in Korean male and female (2006–2019).

As in Taiwanese female, the markedly increased incidence of lung cancer in South Korean female, especially in the early stages, may be due to overdiagnosis resulting from LDCT lung cancer screening, which has been popularized since the early 2000s.

Several risk factors other than smoking, such as age, family history of lung cancer, personal history of cancer, secondhand smoking, indoor and outdoor air pollution, exposure to environmental or occupational lung carcinogens, and pulmonary diseases, have been implicated in causing lung cancer [7]. A quantifiable risk assessment model for never-smokers should be established for population-based screening programs. A previous study that aimed to identify high-risk never-smokers through lung

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cancer screening suggested that never-smokers with high relative risks might have trade-offs between benefits and harms that are similar to those of smokers undergoing lung cancer screening, according to the US Preventive Services Task Force guidelines [8]. However, none of the 65711 never-smokers in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial had a high risk according to the PLCO model [9], and only 0.04% (4 of 10697) of never-smokers had a high risk and were eligible for the UK Lung Cancer Screening Trial [10]. However, these estimations are based on data from the Western population and may not apply to East Asian never-smokers. Accordingly, widespread LDCT screening is not recommended in never-smokers unless new evidence emerges to support such a process.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Jin Mo Goo received research grants from Infinitt Healthcare, Dongkook Lifescience, and LG Electronics, outside the present study. Jin Mo Goo who is on the editorial board of the *Korean Journal of Radiology* was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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Funding Statement

None

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 https://doi.org/10.3348/kjr.2022.0190