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Association between Muscle Mass and the Risk of Incident Lung Cancer in Never-smokers

근육 량과 비흡연자 폐암 발생 위험 간의 연관성

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서울대학교 대학원
의학과 내과학 전공

김 소 연

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지도교수 이상민

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서울대학교 대학원
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김 소 연

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위원장 _____(인)
부위원장 _____(인)
위원 _____(인)

Abstract

Background: Lung cancer in never-smokers (LCINS) is an emerging global health concern since its prevalence and disease burden continuously increase within the poorly understood etiology. Body composition abnormalities are major preventable risk factors for various cancer. However, their role in incident LCINS diagnosis remains uninvestigated. Detectable body composition abnormalities might be important modifiable etiologic factors for LCINS. We aimed to evaluate the association of muscle mass, subcutaneous, and visceral adiposity with the risk of incident LCINS diagnosis.

Methods: This cross-sectional case-control study used prospectively collected data derived from a readily approved ongoing LCINS cohort. Body compositions of 326 newly-diagnosed LCINS patients and 348 never-smoker controls were analyzed via deep-learning-based automated volumetric analysis of unenhanced torso computed tomography images. The cross-sectional area at the third lumbar vertebra and waist-level volume of muscle and fat were quantified, then normalized by height to generate skeletal muscle index, fat index, skeletal muscle volume index (SMVI), and fat volume index. Sarcopenia was defined as reduced skeletal muscle index (men, <55 cm^2/m^2; women, <39 cm^2/m^2). Odds ratios (ORs) of

LCINS were estimated using sex-specific, mutually-adjusted generalized additive and linear logistic regression models. Age-matched sensitivity analysis was performed using univariable and multivariable conditional logistic regression models.

Results: LCINS patients (n=326; 44[13.5%] men) were older (mean ± SD age, men, 65.2 ± 12.4 years vs 58.7 ± 9.9; women, 64.5 ± 9.9 vs 53.9 ± 10.3) and more often presented with sarcopenia (men, 77.3% vs 41.2%; women, 43.3% vs 23.6%) than controls (n=348; 68 [19.5%] men). The risk of incident LCINS decreased in a dose-response manner with increased skeletal muscle index (men, adjusted OR [aOR] 0.89, 95% CI 0.83–0.94; women, aOR 0.86, 95% CI 0.83–0.89). The aORs of incident LCINS for men and women in the lowest quartile of skeletal muscle index were 12.71 (p=0.002) and 20.52 (p<0.001), respectively, compared with those in the highest quartile. Similar patterns were observed for SMVI. Sarcopenia was strongly correlated to incident LCINS (men, aOR 6.28; women, aOR 4.32; both p<0.001). No adiposity measures showed meaningful associations with incident LCINS diagnosis. Sensitivity analysis strengthened these results.

Conclusion: Muscle mass demonstrated a strong, independent, dose-response inverse relationship with the risk of incident LCINS

diagnosis. Reduced muscle mass might be an easily-detectable and potentially modifiable clinical indicator for incident LCINS.

Keywords: Body composition; Lung cancer in never-smokers; Muscles; Risk; Sarcopenia.

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Introduction

1.1. Study Background

Lung cancer in never-smokers (LCINS) is an emerging global health concern as its prevalence and disease burden continue to rise within largely limited etiologic understanding[1]. Although various etiologic factors including pre-existing oncogenic mutations, familial history of lung cancer, environmental exposures to second-hand smoke, in and outdoor air pollution, radon, asbestos, cooking fumes, and occupational carcinogens have been studied, a thorough understanding of the LCINS tumorigenesis is lacking, and much little is known about individual-level modifiable factors such as body composition abnormalities[2,3].

Body composition abnormalities are major preventable causal risk factors for various cancer[4]. Inadequate amount or distribution of adipose tissue or muscle mass constitutes the second most dominant modifiable etiologic factor for cancer[5]. Epidemiologic studies reported that 7.8% of incident cancer worldwide are attributable to body composition abnormalities[6]. Specifically, excess visceral adiposity or low muscularity induces a pro-carcinogenic environment by promoting chronic inflammation, insulin resistance, hormonal imbalance, and perturbing immuno-metabolism[7,8].

Adding to this evidence, recent studies advocate that detectable body composition abnormalities might also be unique early symptom signatures for incident cancer diagnosis[9]. Despite robust clinical relevance, their impact on incident LCINS diagnosis remains uncertain owing to several issues, including research emphasis on identifying external carcinogens, limited sample size and disparities due to disproportionate representations of LCINS across racial or ethnic groups, methodological challenges arising from the use of indirect or self-reported anthropometric measures, and a predominant focus on adiposity at the expense of muscle mass[10,11].

Traditionally, adiposity was considered the main determinant in the body composition–LCINS relationship given the causal relationship between obesity and cancer[12]. However, previous studies on adiposity using body mass index (BMI)[13], waist circumference (WC), waist-to-hip ratio, and computed tomography (CT)-based two-dimensional (2D) fat measurements generated conflicting evidence and were insufficient to explain how body composition relates to incident LCINS[14,15].

Recently, accumulating evidence highlights that muscles might play a central role in cancer development and progression. Muscle emerged as a key immune-modulatory metabolically-active endocrine organ comprising > 40% of body weight, regulating systemic inflammation,

homeostasis, antitumor activities, tumor cell metabolism, and proliferation[16–18]. In patients with lung cancer, lower muscle mass serves as a major poor prognostic indicator affecting treatment outcomes, morbidity, and mortality[19]. Muscle restoration is also a promising therapeutic target with demonstrated improvements in lung cancer–related outcomes[20].

Although the significance of muscle mass in the later trajectory of lung cancer has been well–established, its association with incident LCINS diagnosis remains uninvestigated. As mentioned earlier, LCINS presents a substantially disproportionate susceptibility across various racial/ethnic and sexual groups[21]. Interestingly, the most vulnerable subgroup to LCINS—Asian women—exhibit the lowest skeletal muscle mass compared to any other populations with equivalent age and BMI[22]. Based on the addressed muscle–lung cancer relationship and the unique epidemiology of LCINS, we hypothesized that muscle mass might be associated with the risk of incident LCINS as a modifiable clinical marker. We also hypothesized that understanding both the individual role and combined effect of muscle, visceral, and subcutaneous adiposity on incident LCINS could address the existing knowledge gap.

CT is the current gold standard for body composition analysis[23]. Anthropometric measures derived from artificial intelligence-engrafted clinically-acquired CTs have great potential to elucidate pre-symptomatic abnormalities that might serve as novel risk factors for cancer[24,25].

1.2. Purpose of Research

This is the first comprehensive body composition analysis targeting LCINS by using CT-based deep-learning-assisted three-dimensional (3D) quantification techniques. We aimed to evaluate associations of muscle mass, subcutaneous, and visceral adiposity with the risk of incident LCINS diagnosis.

Methods

2.1. Study Design and Participants

We conducted a cross-sectional case-control study using data from 1) a prospectively-registered ongoing LCINS cohort (Institutional IRB no. 1301-018-454) at an academic tertiary hospital, and 2) a health-screening database at an affiliated health check-up center.

Eligible case-patients included never-smokers aged ≥ 18 years with the first pathological diagnosis of primary lung cancer (International Classification of Diseases, 10th revision, C34) of any stage and whole-body ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomographic (PET)/CT at diagnosis between January 2013 and December 2017 at Seoul National University Hospital (SNUH). Case-patients were selected from a longitudinal LCINS cohort that prospectively recruited newly-diagnosed LCINS patients during the aforementioned period.

Controls were composed of never-smokers aged ≥ 18 years who voluntarily underwent ^{18}F-FDG-PET/CT as part of self-referred health examinations at SNUH Healthcare System Center, between February 2004 and June 2012. During this period, the study center offered low-cost self-referred or opportunistic cancer screening programs using

PET/CT targeting healthy individuals. Exclusion criteria for controls were: 1) incomplete clinical or anthropometric information, 2) cancer history within 5 years, 3) suspicion of cancer during the health check-up, 4) documented lung nodules, 5) metal or motion artifacts in CT images, and 6) lack of analyzable CT images. Controls were assuredly free of LCINS and other malignancies by screening PET/CTs. The Institutional Review Board of SNUH approved this study and waived the requirement for informed consent.

2.2. Data Collection

We obtained information on case-patients including sex, age, smoking history, histologic subtype, and 7^{th} edition American Joint Committee on Cancer TNM stage at diagnosis. Weight and height were measured at the study center at the time of diagnosis before treatment initiation. In controls, smoking and cancer history were collected via systematic questionnaires. Weight and height were measured at the study center on the day of PET/CT. BMI was calculated as weight in kilograms divided by height in square meters and classified using the World Health Organization (WHO) criteria: under-weight, normal-weight, over-weight, and obese ($BMI < 18.5$; $18.5 \leq BMI < 25$; $25 \leq BMI < 30$; $BMI \geq 30$ kg/m^2).

2.3. Body Composition Analysis

All PET/CTs were performed as conventional ^{18}F-FDG-PET/CTs, covering the skull base to mid-thigh. Unenhanced CT images were extracted and processed using an FDA approved commercially-available body composition analysis software (Deep Catch, version 1.1.4.X, Medical IP Co. Ltd., Seoul, Republic of Korea)[26]. This software contained 3D U-Net that was trained using a total of 39,268 image slices and provided an average dice similarity score of 96.8-99.2% for muscle, 95.1-98.9% for visceral fat, and 97.1-99.7% for subcutaneous fat in the domestic external validation sets, respectively[27]. Deep-learning-based automated body composition segmentation was performed (Fig. 1), and its quality was verified by an experienced radiologist (SHY) with a 16-year clinical experience blinded to clinical information. As in many prior studies, cross-sectional areas of muscle and fat were calculated in the middle of the third lumbar vertebra (L3) regarding its proven correlation with whole-body composition[28]. Because of the time-consuming nature of image-based manual body composition segmentation, single-section body composition quantification was common in the past. However, since 1) both the adipose tissue and muscle mass vary dramatically at different

levels of the abdomen (as much as twofold for muscle and threefold for visceral adipose tissue), and 2) contents of the gastrointestinal tract are constantly shifting, there are growing expectations that 3D analysis at the abdominal level might more accurately represent the whole-body composition[29]. In this study, volume measurements of each body composition were uniformly quantified at waist level (between the lowest rib border and the iliac crest) following the WHO definition[30] and considering the 1) well-established various health impact of abdominal fat tissues[31] and 2) importance of trunk muscle in functional performance in the trajectory of aging[32]. When the patients' arms were included in the L3 or waist level, body compositions were calculated after excluding the arms. The resulting measurements were normalized by height, as is conventional for BMI and other body composition measures[33]. L3 cross-sectional areas of skeletal muscle (cm^2), total fat (cm^2), subcutaneous fat (cm^2), and visceral fat (cm^2) divided by height in square meters generated skeletal muscle index (cm^2/m^2), total fat index (cm^2/m^2), subcutaneous fat index (cm^2/m^2), and visceral fat index (cm^2/m^2). Waist level volumes of skeletal muscle (cm^3), total fat (cm^3), subcutaneous fat (cm^3), and visceral fat (cm^3) divided by height in square meters yielded skeletal muscle volume index (SMVI) (cm^3/m^2), total fat volume index (FVI)

(cm^3/m^2), subcutaneous FVI (cm^3/m^2), and visceral FVI (cm^3/m^2). Sarcopenia was defined as a reduced skeletal muscle index with cut-off values of 55 cm^2/m^2 for men and 39 cm^2/m^2 for women[34-36]. WC was measured at the umbilicus level[37]. Central obesity was defined by the WHO criteria: WC $\geq$ 94 cm for men, and $\geq$ 80 cm for women.

2.4. Statistical Analysis

Men and women were separately analyzed, given their heterogeneity in body composition. Baseline characteristics were compared via standardized mean difference (SMD), where $-0.1 \leq SMD \leq 0.1$ was considered non-significant. Dose-response associations between body composition measures and the risk of incident LCINS were evaluated using generalized additive models testing for nonlinearity. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using generalized linear logistic regression models with a reasonable assumption of linearity. Each body composition measure was assessed in a separate model, with covariates selected based on prior evidence, biological plausibility, and univariable confounder analysis. We presented two final models each adjusted for 1) age and BMI (Model 1)[38], 2) age, BMI, skeletal muscle index, and visceral fat index (Model 2)[39-42].

Skeletal muscle index, SMVI, fat index, and FVI (continuous variables) were further categorized into quartiles based on the study population distribution. Trends across quartiles were tested by treating each quartile as an ordinal variable in multivariable analysis.

To control the effects of age on body composition and incident LCINS, sensitivity analysis was conducted in the age-matched population (± five years). Conditional logistic regression models adjusted for previously mentioned covariates were fitted. Two-sided p-values < 0.05 were considered statistically significant. Statistical analyses were performed using R, version 4.1.2 (R Foundation) and SAS, version 9.4 (SAS Institute).

Results

Among 358 patients in the LCINS cohort, we identified 326 case-patients with analyzable CT scans (Fig. 2). Within 1,099 never-smokers who voluntarily underwent PET/CT as a self-referred health check-up, 751 were excluded for reasons listed in Figure 2. The remaining 348 participants were included as controls without additional selection. Since a significant portion of individuals was excluded during the control enrollment process by not meeting the eligibility criteria, we compared the sex distributions, mean age, and BMI between the 1099 control candidates and 348 controls (919 [83.7%] women vs 280 [80.5%]; mean ± SD age, 51.2 ± 8.8 years vs 53.9 ± 10.3; mean ± SD BMI, 23.7 kg/m^2 ± 3.5 vs 22.6 ± 2.9) and found no statistically significant differences (Table 1). This supported the representativeness of our control subjects and minimized the selection bias.

3.1. LCINS Cohort

The LCINS cohort comprised a total of 358 patients. The mean ± SD age at diagnosis was 64.9 ± 10.3 years, and 296 (82.7%) were women. Adenocarcinoma comprised 91.9% of histologic subtypes. Among patients

with available stage information, the most common stage at diagnosis was stage I (36.0%), followed by stages IV (34.4%), III (18.7%), and II (10.9%). The prevalence of major oncogenic driver mutations was assessed among patients who performed pertinent tissue analysis. 43.6% (129 among 296 patients) harbored activating mutations in the Epidermal Growth Factor Receptor (EGFR), 5.8% (17 among 295 patients) presented with Anaplastic Lymphoma Kinase (ALK) rearrangements, and 9.3% (12 among 117 patients) carried Kirsten RAt Sarcoma (KRAS) mutations.

3.2. Baseline Characteristics

Table 2 shows the baseline characteristics of the study population. Case-patients were older than controls (mean ± SD age; men, 65.2 ± 12.4 years vs 58.7 ± 9.9; women, 64.5 ± 9.9 vs 53.9 ± 10.3) and more often had sarcopenia (men, 77.3% vs 41.2%; women, 43.3% vs 23.6%). In men, case-patients presented a lower average BMI than controls (24.1 ± 2.7 kg/m^2 vs 24.5 ± 2.7), yet the difference in the incidence of central obesity (52.3% vs 52.9%) was insignificant. In women, case-patients had a higher average BMI (24.1 ± 3.6 kg/m^2 vs

22.6 ± 2.9) and more often had central obesity than controls (72.0% vs 48.9%).

3.3. Unadjusted Association of Body Composition Measure with Incident LCINS

The unadjusted associations between body composition measures and incident LCINS were examined using spline models (Fig. 3). In men, age > 65 years positively correlated with LCINS (OR 1.06, 95% CI 1.02–1.10). Skeletal muscle index (OR 0.91, 95% CI 0.87–0.96) and SMVI (OR 0.99, 95% CI 0.99–1.00, p = 0.034) were inversely related to LCINS. No adiposity parameters showed meaningful relationships with LCINS. In women, aging positively correlated with LCINS (OR 1.11, 95% CI 1.09–1.13). Skeletal muscle index (OR 0.93, 95% CI 0.91–0.95) and SMVI (OR 0.99, 95% CI 0.99–1.00, p < 0.001) showed an inverse relationship with LCINS. Visceral fat index (OR 1.04, 95% CI 1.03–1.05) and visceral FVI (OR 1.00, 95% CI 1.00–1.00, p < 0.001) positively correlated with LCINS. Sarcopenia was significantly linked to LCINS, which association appeared stronger for men (OR 4.86, 95% CI 2.07–11.42) than women (OR 2.47, 95% CI 1.72–3.55).

3.4. Adjusted Association of Body Composition Measure with Incident LCINS

Adjusted generalized additive models demonstrated clear dose-dependent inverse relationships between muscle measures and the risk of incident LCINS (Fig. 4). After adjusting for age, BMI, and visceral fat index, a 1-unit increase in skeletal muscle index related to an 11% (adjusted OR [aOR] 0.89, 95% CI 0.83–0.94) and 14% (aOR 0.86, 95% CI 0.83–0.89) reduced LCINS risk in men and women, respectively. Similar patterns, stronger for women, were observed for SMVI. Although suggestive of an inverse relationship, aORs were not estimated for SMVI in men because linearity was not assumed. In women, LCINS risk decreased by 5% per every 10-unit increase in SMVI until 400 cm^3/m^2 (aOR 0.95, 95% CI 0.93–0.98).

Mutual adjustment strengthened the positive correlation between sarcopenia and incident LCINS (men, aOR 6.28, 95% CI 2.27–19.38; women, aOR 4.32; 95% CI 2.69–7.05) (Table 3). The aORs of LCINS were 12.71 (95% CI 2.82–68.88) and 20.52 (95% CI 9.68–45.77), respectively, for men and women in the lowest quartile of skeletal muscle index compared with those in the highest quartile. Similarly, men and women in the lowest quartile of SMVI had aORs of 2.37 (95% CI 0.60–9.87) and

6.86 (95% CI 3.62–13.29), respectively, compared with those in the highest quartile.

No significant associations occurred between adiposity measures and incident LCINS. In women, visceral fat index (aOR 1.02, p = 0.12) and visceral FVI (aOR 1.00, p = 0.08) lost a meaningful relationship with LCINS after adjusting for age, BMI, and skeletal muscle index.

3.5. Sensitivity Analysis

Table 4 shows the baseline characteristics of the age−matched population. Even after age−matching, case−patients more frequently had sarcopenia (men, 73.0% vs 51.4%; women, 40.9% vs 22.2%). Through mutual adjustment, the inverse relationship between muscle measures and incident LCINS became more evident, and it was feasible to assume linearity for every model (Fig. 5). A 1−unit increase in skeletal muscle index related to a 15% (aOR 0.85, 95% CI 0.75–0.96) and 16% (aOR 0.84, 95% CI 0.78–0.89) decreased LCINS risk in men and women, respectively. Every 10−unit increase in SMVI related to a 7% (aOR 0.93, 95% CI 0.88–0.98) and 5% (aOR 0.95, 95% CI 0.92–0.98) reduced LCINS risk in men and women, respectively. Sarcopenia was significantly associated with incident LCINS (men, aOR 5.93, 95% CI 1.22–28.84; women, aOR 4.66,

95% CI 2.34–9.26) (Table 5). The odds of LCINS were more than 40 times higher for individuals in the lowest quartile of skeletal muscle index than those in the highest quartile (men, aOR 60.21, 95% CI 2.61–1391.27; women, aOR 45.00, 95% CI 10.42–194.38). Individuals in the lowest quartile of SMVI had higher odds of LCINS compared to those in the highest quartile (men, aOR 2.11, 95% CI 1.02–4.37; women, aOR 9.76, 95% CI 3.67–25.94).

Discussion

This is the first comprehensive volumetric body composition analysis in LCINS suggesting a strong independent inverse relationship between muscle mass and incident LCINS risk. Individuals in the lowest quartile of skeletal muscle index had over 12 times higher odds of LCINS compared with those in the highest quartile. Promisingly, higher muscle mass was somewhat protective against LCINS. Approximately 13% risk reduction was observed following every 1-unit increase in skeletal muscle index. Our findings were strengthened by: 1) a clear dose-response relationship, 2) consistency through areal and volumetric analyses, 3) stability across gender, and 4) consolidated association after controlling for potential confounders. We found no evidence of meaningful associations between the amount or distribution of adiposity and incident LCINS. Our data imply that individuals with lower muscle mass might have significantly higher chances of LCINS. Moreover, CT-based muscle mass might be an easily-measurable modifiable clinical marker for LCINS.

To our knowledge, this study is the first to investigate the separate and combined effect of muscle, subcutaneous, and visceral fat mass on incident LCINS by using CT-based deep-learning-assisted automated 3D

analysis. We overcame methodological limitations associated with indirect or 2D anthropometric measures[43]. In an attempt to identify clinically applicable modifiable etiologic factors for LCINS, we focused on body composition abnormalities in the earlier disease trajectory—which has been underappreciated—and revealed a strong, independent, dose-response inverse relationship between muscle mass and incident LCINS risk. Our results are of significance since muscle mass is an individual-level modifiable factor that can be conveniently assessed by using artificial intelligence-based CT analysis, given the limited knowledge of preventable factors and clinically applicable biomarkers for LCINS. Our data also provide novel insights about incorporating CT-based body composition measures into identifying subjects at greater risk, guiding personalized screening and prevention strategies, and reducing the growing disease burden of LCINS.

Our findings align with recent evidence suggesting a beneficial effect of muscles against the development of lung cancer. Large prospective cohort studies reported an inverse association of lean body mass with incident lung cancer[44]. A meta-analysis demonstrated that muscle enhancement dose-dependently lowers lung cancer risk[45]. A nationwide cohort study in Taiwan revealed pre-existing sarcopenia to be an independent risk factor

for lung cancer[46]. While this evidence was established in smoking-unstratified, mainly ever-smoker lung cancer patients by using indirect anthropometric measures, we validated this relationship in LCINS by directly-quantified 3D measures.

An inverse relationship between muscle mass and cancer risk has also been found in other cancers. Observational studies reported greater chances of colorectal cancer in individuals with sarcopenia[47,48]. Muscle mass restoration via resistance training lowered the risk of urogenital cancer[49]. Our results of absent relations between adiposity and incident LCINS are consistent with prior evidence. Powered prospective studies showed that the inverse relationship between adiposity and lung cancer risk disappears in never-smokers[50,51]. Our findings suggest that muscle mass rather than adiposity might dominantly correlate to incident LCINS. Our findings are consistent with the epidemiologic characteristics of LCINS, which demonstrate a disproportionately higher burden on Asian women[52]. Asian never-smokers are at significantly greater risk of developing lung cancer compared to other ethnicities[53]. Interestingly, those who represent the most vulnerable demographic to LCINS have the lowest skeletal muscle mass compared to other populations with similar age and BMI[54].

Convincing evidence highlights the crucial role of muscle in cancer trajectories, particularly in patients with lung cancer. Muscle loss accelerates tumor aggressiveness while muscle enhancement delays cancer progression[55]. In lung cancer patients, lower muscle mass has been identified as a predictor of poor prognosis, regardless of disease stages[56]. It has been associated with an increased risk of treatment-related adverse events, disease recurrences, and decreased overall survival[57,58]. Moreover, muscle restoration serves as a promising therapeutic target to improve cancer-related outcomes[59].

Novel direct and indirect mechanisms mediate the antitumor effects of muscle. Muscles secrete myokines (e.g., Oncostatin M, Irisin, and SPARC) that suppress tumorigenesis and induce tumor cell apoptosis[60]. Recent evidence found muscles to be the key source of cytokines (e.g., interleukin-6,7,15, and leukemia-inhibitory factor) that promote anti-cancer immune reactions[61,62].

Our study had limitations. First, although suggestive, it is beyond our study scope to deduce a causal relationship between muscle loss and LCINS. As other factors (e.g., diet and physical activity) leading to muscle loss might play an etiological role, additional studies are needed to clarify the causal relationship. Second, selection bias may affect the

generalizability of our results. Our controls may engage in healthier behaviors and have better access to health services. To reduce selection bias, we minimized judgment in control enrolment. Third, we were unable to adjust for potential confounding effects of other environmental risk factors for LCINS. Fourth, reverse causation may have affected the results. To prevent potential bias resulting from muscle wasting following LCINS progression, we investigated the prevalence of sarcopenia in four stages; Ⅰ 43.5%, Ⅱ 31.4%, Ⅲ 50%, Ⅳ 56.9%, and found a comparable incidence of muscle loss between the early-, total-, and late-stage patients. Fifth, it should be noted that the enrollment period for our LCINS cohort spanned from 2013 to 2017. Consequently, subsequent changes in the stage distribution of LCINS patients among Korean women have been reported, thereby potentially limiting the representativeness of our case patients in reflecting the current LCINS patient population. Sixth, prior studies have not established concrete evidence regarding the clinical implications and representativeness of abdominal-level muscle mass due to the scarcity of research in this field. Further investigations are warranted to ascertain the clinical implications of waist-level muscle mass. Seventh, the definition of sarcopenia in this study was based on Canadian population criteria and optimized for mortality prediction using

lumbar muscle measurements. It may not align with the broader understanding of sarcopenia that encompasses muscle power and mass reduction, and may limit generalizability, accuracy in identifying sarcopenia.

In conclusion, muscle mass had a clear, independent, dose–response inverse relationship with the risk of incident LCINS diagnosis. Muscle mass measured by opportunistic CT scans might be a promising modifiable clinical indicator for LCINS.

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국문 초록

배경: 비흡연자 폐암의 유병률과 질병 부담은 전세계적으로 계속해서 증가하는 추세이나, 그 원인 및 예방 가능한 인자에 대해서는 잘 알려져 있지 않다. 체성분 이상 (비만, 복부 비만, 근 감소증, 근 감소형 비만 등) 은 다양한 암의 중요한 위험인자로 알려져 있으나, 비흡연자 폐암 발생 혹은 초기 진단과의 관련성은 밝혀져 있지 않다. 본 연구는 체성분 이상과 비흡연자 폐암 초기 진단 간 관계를 평가하기 위해 수행되었다.

방법: 본 연구는 단면적 환자-대조군 연구로서, 전향적으로 모집한 326 명의 새로 진단된 비흡연자 폐암 환자와 348 명의 비흡연자 건강 대조군을 대상으로, 양 군의 체성분을 비교 분석하여 폐암 진단과의 연관성을 살펴보았다. 모든 대상자에게서 복부 전산화 단층촬영 영상을 추출하여, 이를 딥러닝 기술을 기반으로 한 자동화 방식을 통해 분석하였다. 허리 부근에서의 근육, 내장지방, 피하지방의 단면적과 부피를 측정하여 키로 나누어 표준화된 지표인 골격근 지수, 내장지방 지수, 피하지방 지수를 생성하였다. 근감소증은 골격근 지수 저하를 기준으로 정의하였다. 각각의 체성분 지표와 비흡연자 폐암 간 관계는 일반화 가중 및 선형 로지스틱 회귀모델을 사용해 분석하였다.

결과: 비흡연자 폐암 환자들이 정상 대조군에 비해 나이가 더 많았으며, 더 많은 비율로 근감소증을 보였다. 골격근 지수는 비흡연자 폐암 발생 위험과 강한 반비례관계를 보였다. 골격근 지수를 사분화 하였을 때, 최하 사분위에 속한 대상자에서 비흡연자 폐암 위험이 최고사분위에 속한 대상자에 비해 남성에서 12 배, 여성에서 20 배 이상으로 높았다. 근감소증은 비흡연자 폐암과 강한 양의 상관관계를 보였다. 반면, 지방 지표들은 비흡연자 폐암과 유의미한 관계를 보이지 않았다. 이러한 결과는 민감도 분석에서 더욱 두드러졌다.

결론: 근육량은 비흡연자에서 폐암 발생 위험과 독립적인 음의 상관관계를 가진다. 근감소증 및 근육량 감소는 비흡연자 폐암 진단 과정에서 중요한 교정 가능한 유발 인자일 수 있다.

주요어: 체성분, 비흡연자 폐암, 근육량, 위험, 근감소증

학번: 2021-24395

Tables

Table 1. Age, Sex, and BMI distribution between control candidates and controls.

	Controls (N = 348)	Control Candidates (N = 1099)	SMD
Age (y)*	53.9 ± 10.3	51.2 ± 8.8	0.28
Female (%)	280 (80.5)	919 (83.7)	
Height (cm)*	159.3 ± 5.4	162.9 ± 5.3	−0.67
Weight (kg)*	58.5 ± 7.9	60.2 ± 7.1	−0.23
Body mass index (kg/m^2)*	22.6 ± 2.9	23.7 ± 3.5	−0.32

Unless otherwise noted, data are numbers of participants, with percentages in parenthesis.
SMD = standardized mean difference.
* Data are mean ± SDs.

Table 2. Baseline characteristics of the study population.

	Men			Women		
	LCINS (N = 44)	Control (N = 68)	SMD	LCINS (N = 282)	Control (N = 280)	SMD
Age (y)*	65.2 ± 12.4	58.7 ± 9.9	0.57	64.5 ± 9.9	53.9 ± 10.3	1.05
Height (cm)*	166.7 ± 6.4	168.9 ± 5.3	−0.38	154.1 ± 5.5	158.0 ± 5.3	−0.73
Weight (kg)*	67.0 ± 8.9	69.9 ± 8.9	−0.32	57.2 ± 9.3	56.2 ± 7.1	0.12
Body mass index (kg/m^2)*	24.1 ± 2.7	24.5 ± 2.7	−0.14	24.1 ± 3.6	22.6 ± 2.9	0.47
Body mass index, Category						
Underweight (< 18.5)	1 (2.3)	1 (1.5)	0.06	13 (4.6)	17 (6.1)	−0.06
Normal weight (18.5–24.9)	29 (65.9)	43 (63.2)	0.06	157 (55.7)	215 (76.8)	−0.46
Overweight (25–29.9)	13 (29.6)	21 (30.9)	−0.03	99 (35.1)	43 (15.4)	0.47
Obesity (≥ 30)	1 (2.3)	3 (4.4)	−0.12	13 (4.6)	5 (1.8)	0.16
Waist Circumference (cm)*	91.8 ± 18.1	90.6 ± 26.7	0.05	87.6 ± 23.2	73.3 ± 31.0	0.53
Central obesity**	23 (52.3)	36 (52.9)	−0.01	203 (72.0)	137 (48.9)	0.49
Sarcopenia***	34 (77.3)	28 (41.2)	0.79	122 (43.3)	66 (23.6)	0.43

Unless otherwise noted, data are numbers of participants, with percentages in parenthesis.
LCINS = lung cancer in never−smokers; SMD = standardized mean difference.
* Data are mean ± SDs.
** Central obesity was defined with waist circumferences with cut−off values of 94 cm for men and 80 cm for women.
*** Sarcopenia was defined as a reduced skeletal muscle index with cut−off values of 55 cm^2/m^2 for men and 39 cm^2/m^2 for women.

Table 3. Adjusted associations between muscle measures and incident lung cancer in never-smokers.

	Men				Women			
	Model 1* (Age, BMI adjusted)		Model 2** (Age, BMI, Adiposity adjusted)		Model 1* (Age, BMI adjusted)		Model 2** (Age, BMI, Adiposity adjusted)	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Sarcopenia***	5.83 (2.19-17.06)	< 0.001	6.28 (2.27-19.38)	< 0.001	4.41 (2.75-7.19)	< 0.001	4.32 (2.69-7.05)	< 0.001
Muscle measures								
Skeletal muscle index, Quartiles	2.43 (1.51-4.13)	< 0.001	2.46 (1.51-4.27)	< 0.001	2.75 (2.17-3.54)	< 0.001	2.72 (2.14-3.50)	< 0.001
Quartile 1 (< 46.2) (< 37.9)****	12.76 (2.93-66.86)	0.001	12.71 (2.82-68.88)	0.002	21.43 (10.15-47.61)	< 0.001	20.52 (9.68-45.77)	< 0.001
Quartile 2 (< 46.3-53.1) (38.0-42.1)	5.87 (1.64-24.35)	0.009	6.16 (1.68-26.45)	0.009	7.82 (4.03-15.47)	< 0.001	7.63 (3.98-15.17)	< 0.001
Quartile 3 (53.5-61.6) (42.2-48.3)	1.85 (0.49-7.52)	0.37	1.62 (0.41-6.80)	0.49	3.03 (1.62-5.67)	< 0.001	2.95 (1.58-5.61)	< 0.001
Quartile 4 (> 61.7) (> 48.4)	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
SMVI, Quartiles	1.71 (1.13-2.68)	0.01	1.57 (1.01-2.49)	0.048	1.82 (1.49-2.23)	< 0.001	1.88 (1.53-2.31)	< 0.001
Quartile 1 (< 224.6) (< 206.5)****	3.26 (0.88-13.03)	0.083	2.37 (0.60-9.87)	0.22	6.19 (3.30-11.86)	< 0.001	6.86 (3.62-13.29)	< 0.001
Quartile 2 (224.7-312.0) (206.7-252.7)	2.08 (0.67-6.79)	0.21	1.66 (0.50-5.62)	0.40	2.68 (1.52-4.78)	< 0.001	2.75 (1.55-4.95)	< 0.001
Quartile 3 (312.1-363.3) (252.7-302.3)	0.31 (0.07-1.15)	0.09	0.25 (0.06-0.97)	0.05	1.52 (0.87-2.68)	0.15	1.56 (0.88-2.79)	0.13
Quartile 4 (> 363.6) (> 302.3)	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	

aOR = adjusted odds ratio; BMI = body mass index; SMVI = skeletal muscle volume index.
* Model 1 was adjusted for age and BMI
** Model 2 was adjusted for age, BMI, and visceral fat index.
*** Sarcopenia was defined as a reduced skeletal muscle index with cut-off values of 55 cm^2/m^2 for men and 39 cm^2/m^2 for women.
**** Ranges for men and women, respectively, in order.

Table 4. Baseline characteristics of the age-matched population.

	Men			Women		
	LCINS (N = 37)	Control (N = 37)	SMD	LCINS (N = 171)	Control (N = 171)	SMD
Age (y)*	64.0 ± 10.0	63.4 ± 9.6	0.06	59.8 ± 8.7	59.2 ± 8.6	0.07
Height (cm)*	165.8 ± 6.3	168.6 ± 4.8	−0.49	155.3 ± 5.3	156.6 ± 5.2	−0.24
Weight (kg)*	67.3 ± 9.1	69.2 ± 9.5	−0.20	58.6 ± 9.2	56.4 ± 6.8	0.28
Body mass index (kg/m^2)*	24.4 ± 2.7	24.3 ± 2.4	0.06	24.3 ± 3.7	23.0 ± 2.7	0.40
Body mass index, Category						
Underweight (< 18.5)	0 (0.0)	0 (0.0)	-	6 (3.5)	6 (3.5)	0.00
Normal weight (18.5–24.9)	23 (62.2)	24 (64.9)	−0.06	98 (57.3)	131 (76.6)	−0.42
Overweight (25–29.9)	13 (35.1)	12 (32.4)	0.06	57 (33.3)	30 (17.5)	0.37
Obesity (≥ 30)	1 (2.7)	1 (2.7)	0.00	10 (5.9)	4 (2.3)	0.18
Waist circumference (cm)*	92.1 ± 19.4	94.4 ± 29.1	−0.09	87.0 ± 21.9	73.6 ± 34.9	0.46
Central obesity**	18.0 (48.7)	19.0 (51.4)	−0.05	121.0 (70.8)	95.0 (55.6)	0.32
Sarcopenia***	27.0 (73.0)	19.0 (51.4)	0.46	70.0 (40.9)	38.0 (22.2)	0.41

Unless otherwise noted, data are numbers of participants, with percentages in parenthesis.

LCINS = lung cancer in never-smokers; SMD = standardized mean difference.

* Data are mean ± SDs.

** Central obesity was defined with waist circumferences with cut-off values of 94 cm for men and 80 cm for women.

*** Sarcopenia was defined as a reduced skeletal muscle index with cut-off values of 55 cm^2/m^2 for men and 39 cm^2/m^2 for women.

Table 5. Adjusted associations between muscle measures and incident lung cancer in never-smokers in the age-matched population.

	Men				Women			
	Model 1* (Age, BMI adjusted)		Model 2** (Age, BMI, Adiposity adjusted)		Model 1* (Age, BMI adjusted)		Model 2** (Age, BMI, Adiposity adjusted)	
	aOR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value
Sarcopenia* **	6.26 (1.34-29.17)	0.02	5.93 (1.22-28.84)	0.03	4.89 (2.48-9.67)	< 0.001	4.66 (2.34-9.26)	< 0.001
Muscle measures								
Skeletal muscle index, Quartiles	3.07 (1.33-7.09)	0.008	3.19 (1.32-7.74)	0.01	3.09 (2.07-4.63)	< 0.001	3.09 (2.04-4.66)	< 0.001
Quartile 1 (< 46.2) (< 37.9)****	46.93 (2.54-867.14)	0.009	60.21 (2.61-1391.27)	0.01	46.37 (11.02-195.07)	< 0.001	45.00 (10.42-194.38)	< 0.001
Quartile 2 (46.3-53.1) (38.0-42.1)	16.40 (1.32-204.14)	0.03	21.50 (1.44-322.05)	0.03	12.21 (4.21-35.42)	< 0.001	12.31 (4.17-36.34)	< 0.001
Quartile 3 (53.5-61.6) (42.2-48.3)	7.25 (0.81-64.83)	0.08	9.91 (0.94-104.71)	0.06	6.59 (2.35-18.49)	< 0.001	6.36 (2.24-18.06)	< 0.001
Quartile 4 (> 61.7) (> 48.4)	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
SMVI, Quartiles	2.06 (1.11-3.84)	0.02	2.11 (1.02-4.37)	0.045	1.88 (1.41-2.50)	< 0.001	2.10 (1.52-2.89)	< 0.001
Quartile 1 (< 224.6) (< 206.6)****	11.33 (0.89-144.50)	0.06	13.51 (0.61-300.49)	0.20	7.00 (2.91-16.82)	< 0.001	9.76 (3.67-25.94)	< 0.001
Quartile 2 (225.1-312.0) (206.7-252.7)	4.18 (0.77-22.56)	0.10	4.48 (0.71-28.71)	0.11	3.76 (1.66-8.49)	0.001	4.30 (1.80-1.03)	0.001
Quartile 3 (312.8-363.3) (252.8-301.8)	0.32 (0.06-1.63)	0.17	0.34 (0.06-1.82)	0.21	2.50 (1.19-5.27)	0.02	2.58 (1.19-5.58)	0.02
Quartile 4 (> 363.4) (> 301.9)	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	

aOR = adjusted odds ratio; BMI = body mass index; SMVI = skeletal muscle volume index.

* Model 1 was adjusted for age and BMI.

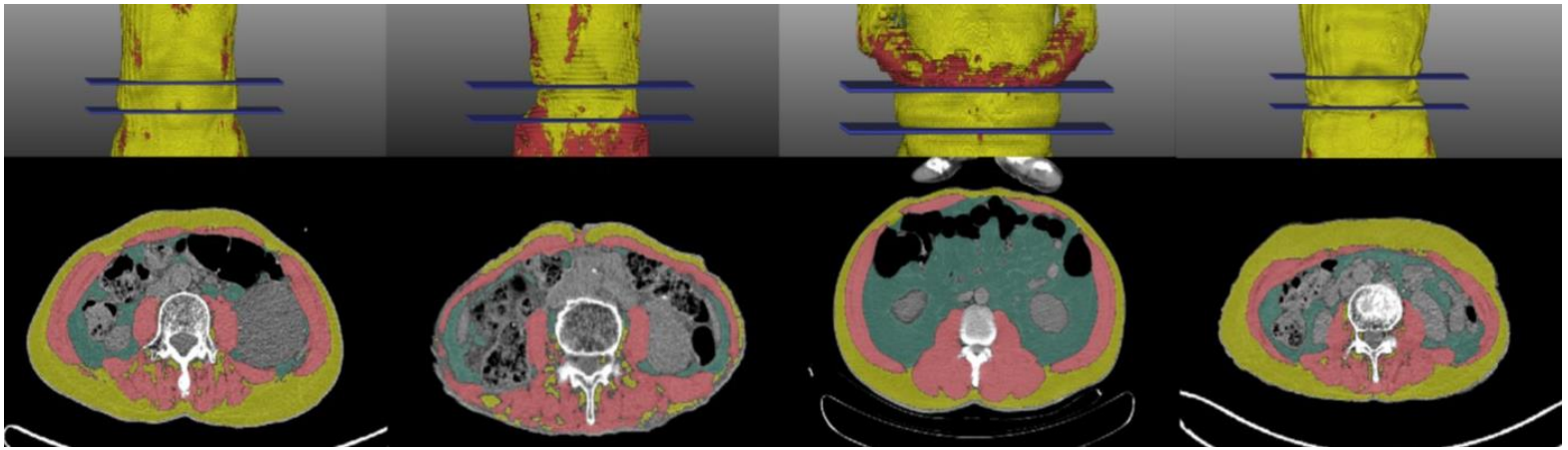
** Model 2 was adjusted for age, BMI, and visceral fat index.

*** Sarcopenia was defined as a reduced skeletal muscle index with cut-off values of 55 cm^2/m^2 for men and 39 cm^2/m^2 for women.

**** Ranges for men and women, respectively, in order.

Figures

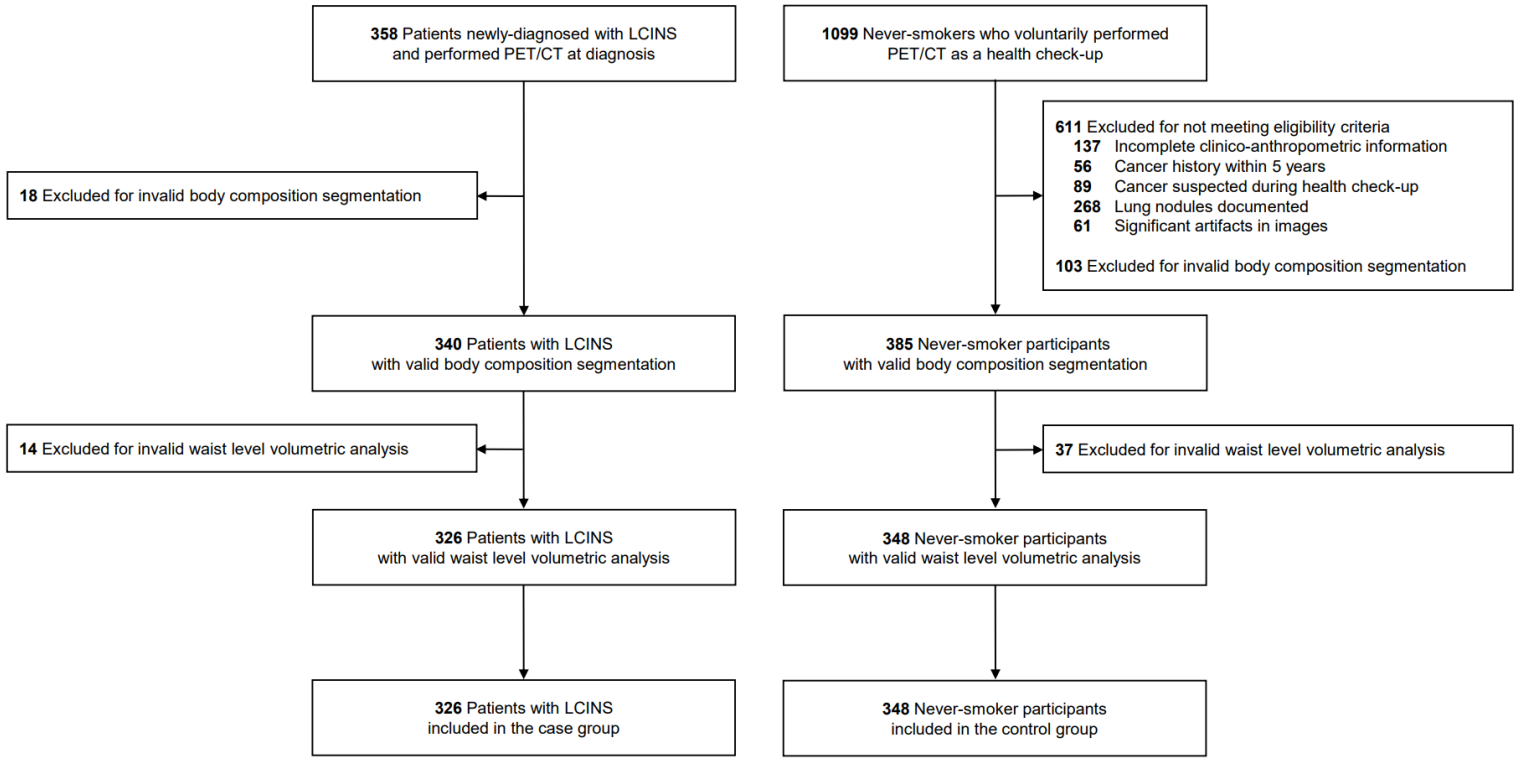
Figure 1. Deep-learning-based automated body composition segmentation using PET/CT-derived CT images.



Deep-learning-based automated body composition segmentation was performed using unenhanced CT scans extracted from PET/CTs. Body components were segmented into skeletal muscle (red), visceral fat (dark green), subcutaneous fat (yellow), as well as skin, bone, internal organs, vessels, and the central nervous system. The waist level was marked by two blue horizontal lines, with the upper line indicating the lowest rib border and the lower line indicating the iliac crest.

PET/CT = positron emission tomographic/computed tomography.

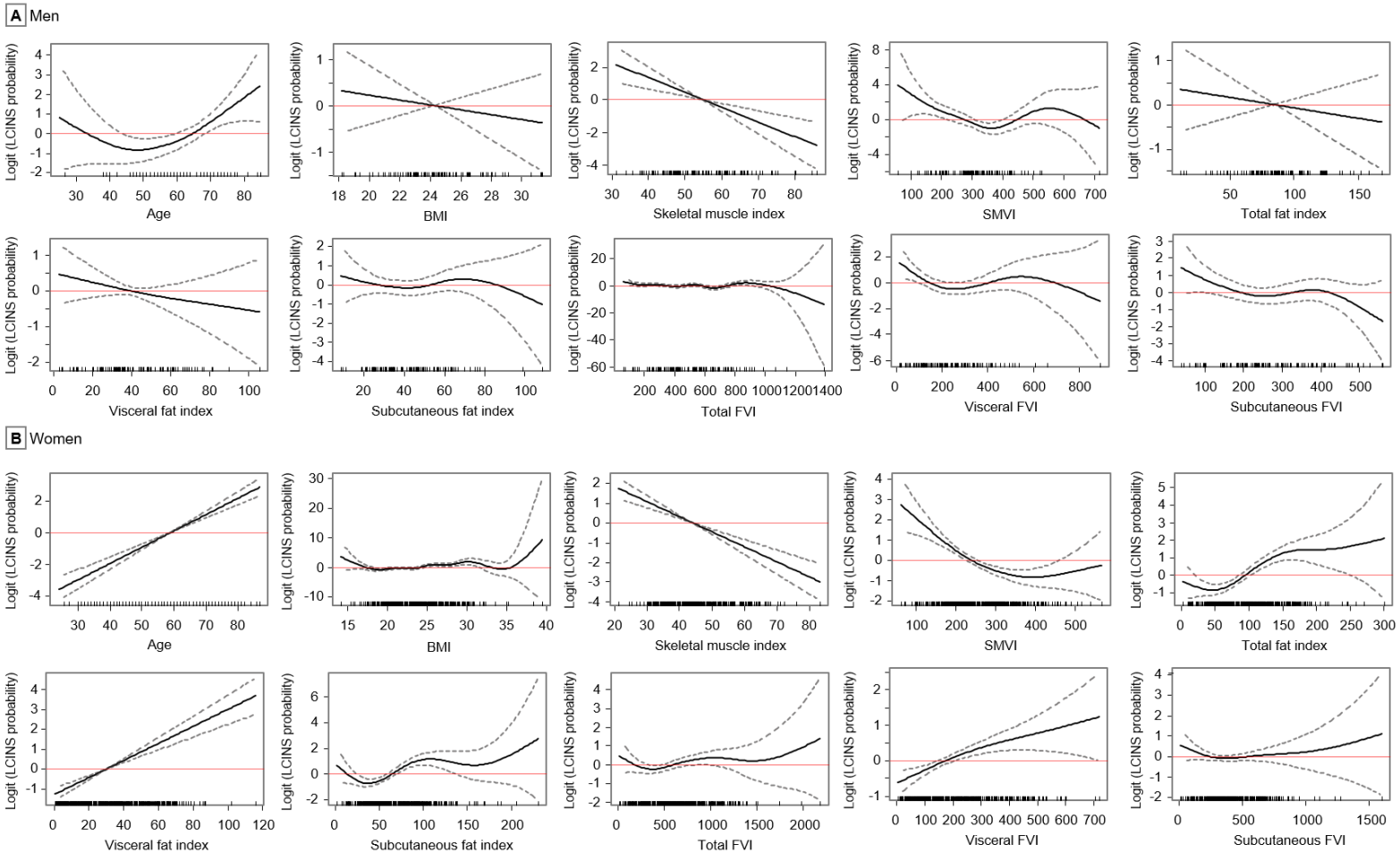
Figure 2. Flow diagram for the inclusion and exclusion criteria.



Our study included 326 newly-diagnosed never-smoker lung cancer patients and 348 never-smoker controls with analyzable CT images.

LCINS = lung cancer in never-smokers.

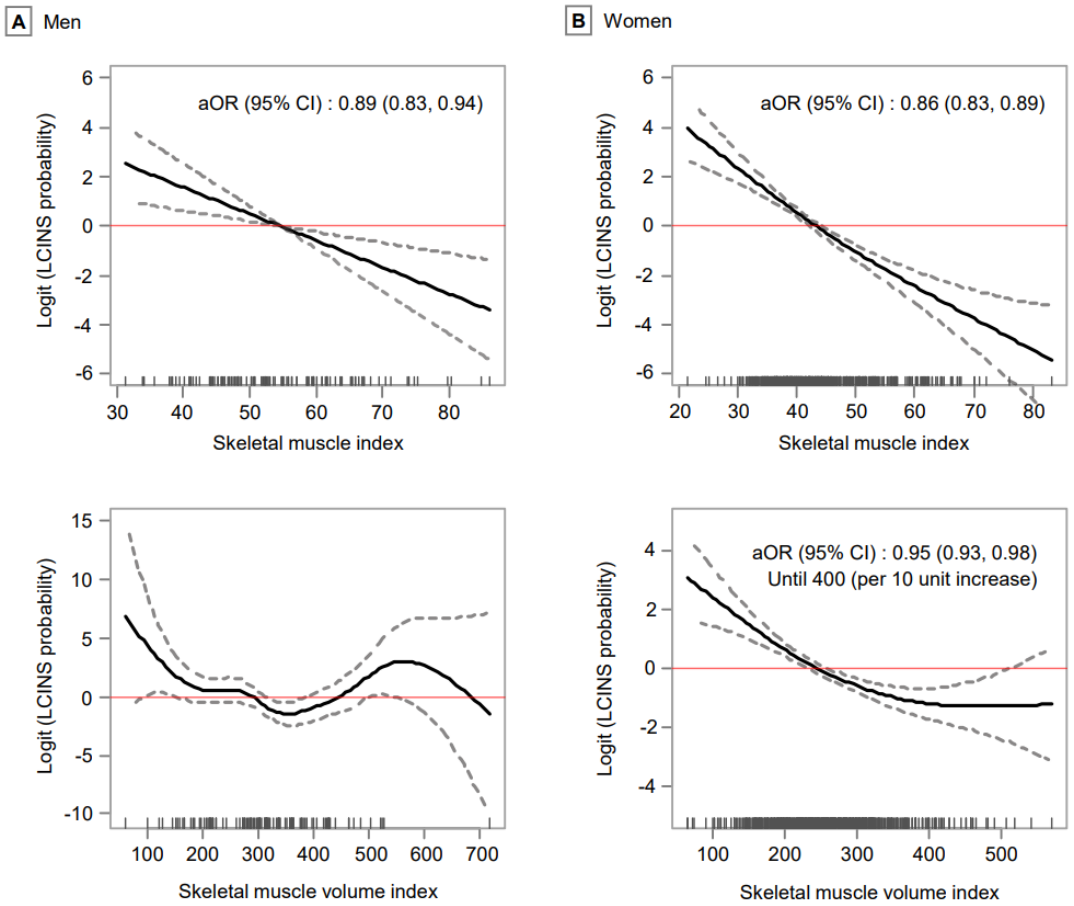
Figure 3. Unadjusted associations between body composition measures and incident lung cancer in never-smokers.



We used separate spline models to depict the continuous association between each body composition measure and the incident diagnosis of lung cancer in never−smokers (LCINS). The grey dashed lines indicate the 95% CIs. Hash marks along the x−axis indicate individual study participants.

BMI = body mass index; FVI = fat volume index; LCINS = lung cancer on never−smokers; SMVI = skeletal muscle volume index.

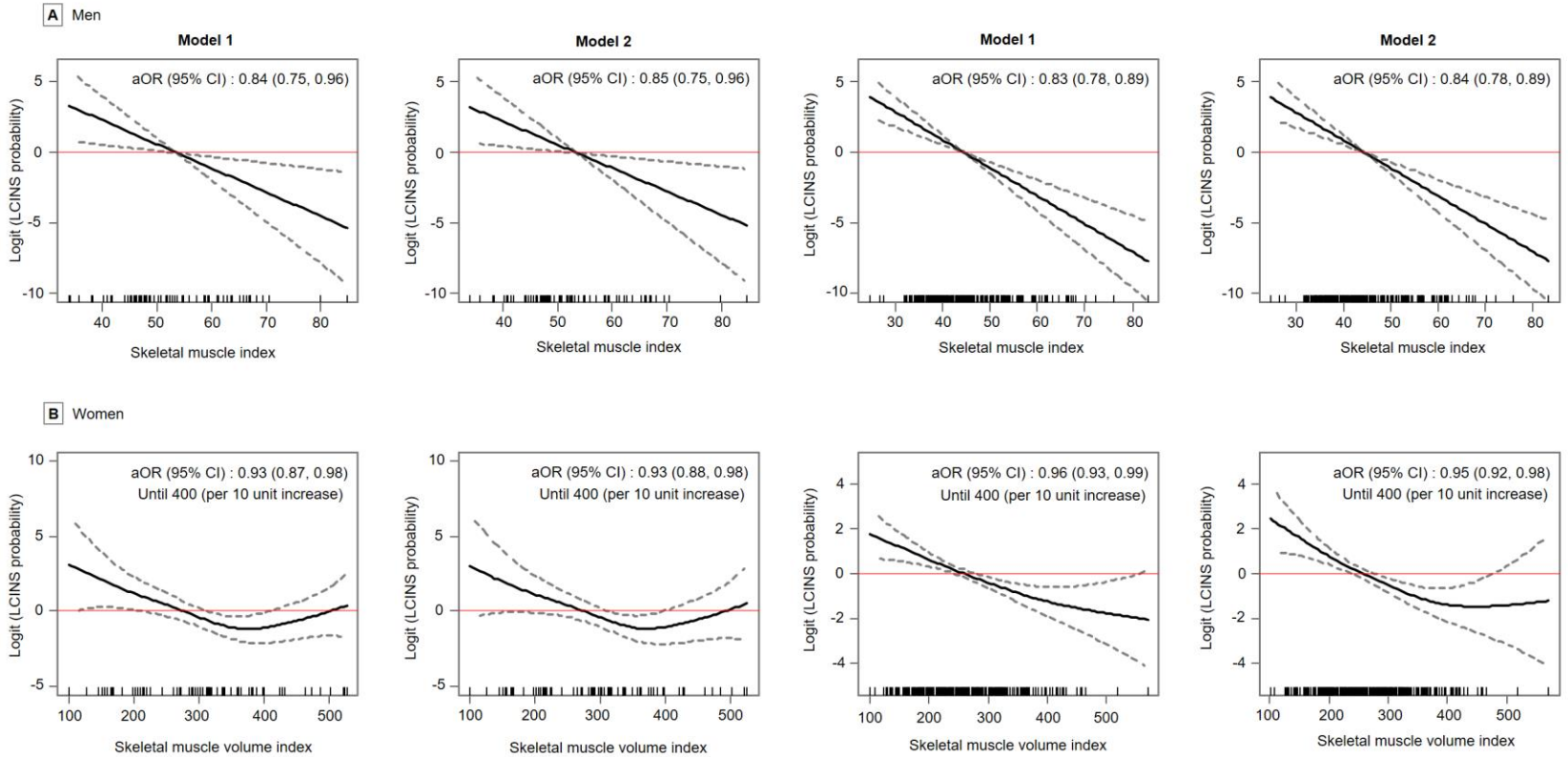
Figure 4. Adjusted associations between muscle measures and incident lung cancer in never-smokers.



We implemented fully adjusted generalized additive logistic regression models to visualize the association between each muscle measure and incident lung cancer in never−smokers (LCINS). Adjusted odds ratios (aORs) with 95% CIs of LCINS were calculated using generalized linear logistic regression models after adjusting for age, body mass index (BMI), and visceral fat index. The aORs for skeletal muscle index are presented per 1−unit increase, while those for skeletal muscle volume index (SMVI) are per 10−unit increase. The grey dashed lines represent 95% CIs. Hash marks along the x−axis indicate individual participants.

aOR = adjusted odds ratio; BMI = body mass index; SMVI = skeletal muscle volume index.

Figure 5. Adjusted associations between muscle measures and incident lung cancer in never-smokers in the age-matched population.



We implemented fully adjusted generalized additive logistic regression models to visualize the association between each muscle measure and the incident diagnosis of lung cancer in never-smokers (LCINS). Adjusted odds ratios (aORs) with 95% CIs of LCINS were calculated using conditional logistic regression models. Model 1 was adjusted for age and body mass index (BMI). Model 2 was adjusted for age, BMI, and visceral fat index. The aORs for skeletal muscle index are presented per 1-unit increase, while those for skeletal muscle volume index (SMVI) are per 10-unit increase. The grey dashed lines represent 95% CIs. Hash marks along the x-axis indicate individual participants. aOR = adjusted odds ratio; BMI = body mass index; LCINS = lung cancer in never-smokers; SMVI = skeletal muscle volume index.