European Journal of Epidemiology (2019) 34:1151–1160
https://doi.org/10.1007/s10654-019-00587-2

CANCER

Predicted lean body mass, fat mass and risk of lung cancer: prospective US cohort study

Su-Min Jeong[1] · Dong Hoon Lee[1] · Edward L. Giovannucci[1,2,3]

Received: 13 September 2019 / Accepted: 14 November 2019 / Published online: 21 November 2019

Abstract

An inverse association between body mass index (BMI) and risk of lung cancer has been reported. However, the association of body composition such as fat mass (FM) and lean body mass (LBM) with risk of lung cancer has not been fully investigated. Using two large prospective cohort studies (Nurses' Health Study, 1986–2014; Health Professionals Follow-up Study, 1987–2012) in the United States, we included 100,985 participants who were followed for occurrence of lung cancer. Predicted FM and LBM derived from validated anthropometric prediction equations were categorized by sex-specific deciles. During an average 22.3-year follow-up, 2615 incident lung cancer cases were identified. BMI showed an inverse association with lung cancer risk. Participants in the 10th decile of predicted FM and LBM had a lower risk of lung cancer compared with those in the 1st decile, but when mutually adjusted for each other, predicted FM was not associated with lung cancer risk (adjusted hazard ratio [aHR] = 0.98, 95% confidence interval [CI] 0.72–1.35; P(trend) = 0.97) whereas predicted LBM had an inverse association (aHR = 0.73, 95% CI 0.53–1.00; P(trend) = 0.03), especially among participants who were current smokers or had smoked in the previous 10 years (aHR = 0.55, 95% CI 0.36–0.84; P(trend) = 0.008). In conclusion, BMI was inversely associated with lung cancer risk. Based on anthropometric prediction equations, low LBM rather than low FM accounted for the inverse association between BMI and lung cancer risk.

Keywords Body mass index · Fat mass · Lean body mass · Lung cancer · Smoking

Introduction

Obesity, typically assessed by body mass index (BMI), is associated with an increased risk of 13 cancers, including breast, endometrial, colorectal and kidney cancers [1]. In contrast, an inverse association of BMI with the risk of lung cancer is seen in many epidemiologic studies [2–7]. This inverse association is more evident in smokers compared to non-significant associations in non-smokers, suggesting that negative confounding by smoking could be the main explanation [2, 4, 5]. Smoking is inversely associated with body weight as well as being a strong risk factor for lung cancer [8, 9]. However, these previous studies had relatively small study sizes [6], limited study population (e.g., women and older adults) [4, 5, 7], and most importantly, BMI may not reflect body composition [2–7].

Although measuring BMI is the most common way to assess the general obesity, it may not adequately capture the differences in body composition and fat distribution, which may differentially effect development of lung cancer. For instance, a higher waist circumference (WC) and a higher

Su-Min Jeong and Dong Hoon Lee have contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10654-019-00587-2) contains supplementary material, which is available to authorized users.

✉ Edward L. Giovannucci
egiovann@hsph.harvard.edu

[1] Department of Nutrition, Harvard T.H. Chan School of Public Health, 665 Huntington Avenue, Boston, MA 02115, USA

[2] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA

[3] Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA

waist to hip ratio (WHR) were positively associated with lung cancer risk in contrary to an inverse association of BMI with lung cancer risk [10, 11]. A large pooled cohort study considered the joint effects of BMI and WC/WHR, and participants who had low BMI (< 25 kg/m^2) and high WC showed the highest hazard ratio of 1.40 (95% confidence interval [CI] = 1.26–1.56) compared to those with high BMI (≥ 25 kg/m^2) and normal WC [10].

Fat mass (FM) and lean body mass (LBM) both contribute to BMI, which is based on body weight regardless of body composition, and are likely to have differential effects on health outcomes [12–14]. Higher FM is generally associated with increased mortality, whereas suboptimal LBM may be associated with increased mortality. In addition, low LBM is related to poor prognosis of cancer and smoking related disease (e.g., chronic obstructive pulmonary disease [COPD]) [15, 16]. The combination of high WC but low BMI may correspond to low LBM.

To our best knowledge, no studies evaluated differential effects of FM and LBM on lung cancer risk. Therefore, examining the independent roles of FM and LBM beyond BMI related to lung cancer risk may improve our understanding of the inverse relationship between BMI and lung cancer risk.

Methods

Study setting and study population

Two ongoing prospective US cohort studies were included in this study. The Nurses' Health Study (NHS) enrolled 121,701 female nurses aged 30–55 years in 1976 and the Health Professionals Follow-up Study (HPFS) enrolled 51,529 male health professionals aged 40–75 years in 1986. All participants were asked to answer the questionnaires related to their demographic, lifestyle and medical information by mailing at baseline and followed up every two years. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. For this study, we excluded those previously diagnosed with cancer or those with extreme BMI (< 12.5 or > 60 kg/m^2) at baseline. A total of 100,985 (62,917 women; 38,068 men) were included in the final analysis.

Exposure measurements: predicted body composition

Predicted FM and LBM were derived using validated anthropometric prediction equations which were developed using a large US representative sample of 7531 men and 6534 women who had a measure of dual energy x ray absorptiometry (DXA) from the National Health and Nutrition Examination Survey (NHANES) [17]. Briefly, FM and LBM measured by DXA were defined as a dependent variable and a linear regression was conducted using age, race, height, weight and WC as independent variables to derive the predicted FM and LBM. High predictive values for FM (men: $R^2 = 0.90$; women: $R^2 = 0.93$). and LBM (men: $R^2 = 0.91$; women: $R^2 = 0.85$) were noted by using the anthropometric prediction equations in an independent validation population [18]. Using the prediction equations, we calculated the predicted FM and LBM for each participant based on their age, race, height, weight and WC. Details on the development and validation of the equations have been described elsewhere and these variables have been used in epidemiologic studies [17, 19, 20].

Outcomes: incidence of lung cancer

Newly diagnosed lung cancers were self-reported by the participants from the biennial questionnaires or identified on their death certificates. The response rate exceeded 90% for each questionnaire. We searched the National Death Index for all non-respondents [21]. To confirm the lung cancer and precise date of diagnosis, medical records and pathology reports were reviewed if participants give permission. When it was not able to review the medical record, we requested data from state cancer registries on detailed information related diagnosed cancer through linking the participant's information. Lung cancers related deaths were identified by death certificates with relevant ICD-8 (international classification of diseases, 8th revision) codes (codes 162) and confirmed through medical records by study physicians. Among the cases with confirmed histology, lung cancer types were classified into adenocarcinoma, squamous and small-cell carcinoma.

Statistical analysis

Cox proportional hazards regression analyses were performed to estimate hazard ratios and 95% CI. Person-years were calculated from the baseline when predicted scores were first available (1986 for NHS; 1987 for HPFS) until the diagnosis of lung cancer or other cancer (except non-melanoma skin cancer), death or the end of observation period (June 2014 for NHS: January 2012 for HPFS). The models with predicted FM was adjusted for height to account for variation of body size. As LBM has a high correlation with height, predicted LBM was adjusted for height by using residuals from the regression of LBM on height. BMI, predicted FM and LBM were categorized into sex-specific deciles. In a multivariable model, we adjusted for age, race, smoking status: never, time since quit smoking among past

smokers, and cigarettes per day among current smokers, alcohol, physical activity and alternate healthy eating index. We also ran an additional model mutually adjusting for predicted FM and LBM in deciles in addition to these potential confounding factors.

To examine whether the association of predicted FM and LBM with lung cancer risk differed by smoking status, we conducted stratified analyses according to the smoking status (never, past and current smokers) and recent exposure to smoking (never + quit smoking at least 10 years and current + smoked in the last 10 years). To investigate the relationship and latency between predicted FM and LBM and lung cancer risk, we performed analysis using various lag times (0, 4+, 8+, 12+ years) by shifting the baseline to 1986 (1987 for HPFS), 1990, 1994 and 1998, respectively, and updating predicted FM and LBM using three repeated measures, accordingly [19]. We conducted analyses separately by sex and pooled the data of women and men after including sex as a stratification variable. All statistical tests were two sided, and a p value < 0.05 was considered to have statistical significance. Statistical analyses were carried out using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

Table 1 depicts the baseline characteristics according to sex and sex-specific BMI deciles. The mean baseline age of the study population was 53.3 years (standard deviation [SD]: 7.5 years) in women and 54.4 years (SD: 9.8) in men. Mean BMI was 25.0 kg/m^2 in women and 25.4 kg/m^2 in men. Participants in higher BMI deciles had higher weight, WC, predicted percent fat, predicted FM and LBM. Participants in the lowest BMI deciles showed the highest percentage of current smokers.

Incidence of lung cancer

During 22.3 years of mean follow-up, 2615 lung cancers (1778 women and 837 men) occurred. In the pooled multivariable adjusted model, BMI was inversely associated with risk of lung cancer incidence. Participants in the highest decile of BMI showed the lowest risk of lung cancer (adjusted hazard ratio [aHR] = 0.73, 95% CI 0.61–0.88), showing significantly decreasing trend as BMI decile increases (P for trend = 0.003) (Table 2). Those in the highest decile of predicted FM and LBM had the lowest risk of lung cancer incidence (aHR = 0.75, 95% CI 0.62–0.90 for predicted FM; aHR = 0.75, 95% CI 0.63–0.90 for predicted LBM) compared with those in the lowest decile groups. When we mutually adjusted for predicted FM and LBM, the associations of predicted FM and LBM with lung cancer risk were weakened. However, the inverse association between predicted LBM and lung cancer risk consistently remained significant, though the confidence intervals widened and the overall p value for trend went from 0.002 to 0.03.

According to the various lag times, we consistently observed an inverse association of BMI and predicted LBM with lung cancer risk (Supplementary table S1). With longer lag times, BMI and predicted FM showed weaker inverse associations with lung cancer risk. In sex-stratified analysis, BMI, predicted FM and LBM were inversely associated with lung cancer risk among women in accordance with our main findings (Supplementary table S2). However, BMI, predicted FM and LBM were not significantly associated with lung cancer risk in men (Supplementary table S3). According to the histologic subtypes of lung cancer, BMI and predicted LBM were inversely associated with risk of adenocarcinoma and squamous cell carcinoma of the lung (Table 3).

Incidence of lung cancer stratified by smoking status

Table 4 shows the association of BMI, predicted FM and LBM with lung cancer risk stratified by smoking status and time since quitting smoking. We observed stronger inverse associations of BMI and predicted LBM with lung cancer risk among current smokers than that of never or past smokers. However, predicted FM was not associated with risk of lung cancer regardless of smoking status in the mutually adjusted models. Among those who currently smoked or had smoked in the previous 10 years, participants in the fourth to tenth deciles of BMI had 15–30% lower risk of lung cancer, compared to those in the lowest decile of BMI. For predicted FM, there was no significant association with lung cancer risk among those who currently smoke or had smoked in the previous 10 years (aHR = 1.13, 95% CI 0.75–1.72). In contrast, the eighth to tenth deciles of predicted LBM were associated with 28–45% lower risk of lung cancer compared to the lowest decile (aHR = 0.55, 95% CI 0.36–0.84 in the tenth decile).

These associations were more robust in women than in men. Among women who currently smoked or smoked in the previous 10 years, BMI had a strong inverse association with lung cancer risk, whereas there was no significant association among women who never or quit the smoking 10 years ago (Supplementary table S4). In these women who currently smoked or smoked in the previous 10 years, predicted FM was not linearly associated with risk, though a U-shape pattern was suggested; predicted LBM displayed a non-significant ($P = 0.12$) inverse association. In contrast, among men who currently smoked or smoked in the previous 10 years, BMI was not linearly associated but a U-shape pattern was suggested,

Table 1 Age standardized characteristics of participants in the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS)

	Body mass index									
	Decile 1	Decile 2	Decile 3	Decile 4	Decile 5	Decile 6	Decile 7	Decile 8	Decile 9	Decile 10
Women (NHS)										
Person-year	68,487	67,890	69,414	66,793	68,283	68,402	67,927	68,654	68,427	68,175
Age (years[a])	52.2	52.3	52.5	52.9	53.1	53.6	53.8	54.1	54.4	54.2
Height (cm)	164.6	164.3	164.0	164.1	164.0	164.1	163.2	164.0	163.4	163.3
Weight (kg)	52.5	56.6	58.8	61.2	63.5	66.2	68.7	73.3	78.7	94.0
WC (cm)	67.8	70.7	72.7	74.9	76.9	79.4	82.0	85.8	90.6	100.6
BMI (kg/m^2)	19.3	20.9	21.8	22.6	23.5	24.5	25.7	27.2	29.4	35.1
Predicted fat mass (kg)	16.2	18.9	20.4	21.9	23.4	25.2	27.0	29.9	33.5	43.3
Predicted percent fat (%)	32.3	33.8	34.7	35.5	36.4	37.4	38.6	40.0	42.2	47.3
Predicted lean body mass (kg)	35.1	36.4	37.2	38.0	38.7	39.7	40.3	42.1	43.8	49.2
Physical activity (MET-h/wk)	18.4	18.0	17.4	16.8	15.9	15.2	14.7	14.1	12.7	11.0
AHEI score	51.3	51.7	52.0	51.9	51.6	51.3	51.5	51.2	50.4	49.6
Alcohol intake (g/day)	7.3	7.2	7.1	7.1	6.7	6.4	5.8	5.5	4.5	3.3
White (%)	99.6	99.5	99.5	99.2	99.1	99.0	98.8	98.8	98.3	98.1
Smoking status (%)										
Never	43.8	44.1	44.0	45.4	45.0	45.8	46.2	45.5	47.6	48.8
Past	40.8	43.1	44.2	43.5	44.1	44.1	44.4	44.9	43.8	44.4
Current	15.3	12.8	11.8	11.2	10.9	10.1	9.4	9.6	8.6	6.7
Men (HPFS)										
Person-year	39,358	38,622	40,760	32,350	39,765	39,507	42,061	38,741	39,447	39,121
Age (years[a])	53.7	53.7	53.8	54.8	54.2	54.1	54.4	54.5	55.0	55.3
Height (cm)	179.1	178.2	178.7	177.9	179.3	178.4	178.4	177.8	178.4	178.3
Weight (kg)	67.5	71.8	75.0	76.2	79.3	80.7	83.2	85.6	90.5	101.7
WC (cm)	85.4	88.3	90.5	91.7	93.5	94.9	96.9	98.8	102.4	111.0
BMI (kg/m^2)	21.0	22.6	23.4	24.0	24.6	25.3	26.0	27.0	28.3	31.9
Predicted fat mass (kg)	14.9	17.1	18.6	19.4	20.7	21.6	22.9	24.3	26.7	32.6
Percent fat (%)	23.1	24.2	24.9	25.5	26.0	26.6	27.4	28.1	29.4	32.7
Predicted lean body mass (kg)	50.7	52.8	54.4	54.9	56.6	57.1	58.3	59.4	61.8	67.1
Physical activity (MET-h/wk)	24.0	24.1	22.7	21.0	21.5	20.0	19.2	18.5	17.4	14.1
AHEI score	54.1	54.3	53.6	54.1	53.5	52.7	52.6	51.8	51.5	50.7
Alcohol intake (g/day)	10.7	11.1	11.3	11.8	11.7	12.2	11.8	11.3	11.9	10.8
White (%)	99.3	99.7	99.3	98.8	99.3	99.4	99.3	99.0	98.8	98.8
Smoking status (%)										
Never	50.4	47.1	45.9	43.8	42.7	39.1	40.6	40.1	37.1	34.4
Past	30.1	35.7	36.8	38.1	38.7	40.5	39.9	37.9	39.9	39.9
Current	9.1	6.0	6.5	6.7	6.7	7.5	6.6	6.9	6.9	6.4

Values are means for continuous variables; percentages for categorical variables, and are standardized to the age distribution of the study population

WC waist circumference, *BMI* body mass index, *MET* metabolic equivalent, *AHEI* alternate healthy eating index

[a]Value is not age adjusted

and predicted FM had a non-significant ($P = 0.08$) positive trend whereas predicted LBM had a non-significant inverse ($P = 0.10$) trend (Supplementary table S5). Among male never smokers, a positive association (P trend = 0.02) was observed with predicted FM.

Joint association of BMI and WC with lung cancer risk

When we examined the joint association of BMI and WC with lung cancer risk, the lowest risk overall and in men

Table 2 Association of body mass index, fat mass and lean body mass with risk of lung cancer (Pooled results of the Nurses' Health Study, 1986–2014 and the Health Professionals Follow-up Study, 1987–2012)

	No of cases	Hazard Ratio (95% CI)		
		Age-adjusted model	MV model	MV + FM/LBM model
BMI				
Decile 1	322	1 (ref)	1 (ref)	NA
Decile 2	251	0.78 (0.66–0.92)	0.85 (0.72–1.00)	NA
Decile 3	287	0.85 (0.72–1.00)	0.97 (0.82–1.13)	NA
Decile 4	227	0.73 (0.62–0.87)	0.84 (0.71–1.00)	NA
Decile 5	262	0.76 (0.65–0.90)	0.88 (0.75–1.04)	NA
Decile 6	275	0.77 (0.66–0.91)	0.90 (0.76–1.06)	NA
Decile 7	296	0.82 (0.70–0.96)	0.96 (0.82–1.13)	NA
Decile 8	240	0.68 (0.57–0.80)	0.80 (0.68–0.95)	NA
Decile 9	262	0.74 (0.63–0.87)	0.90 (0.76–1.06)	NA
Decile 10	193	0.59 (0.49–0.70)	0.73 (0.61–0.88)	NA
P-trend		<.001	0.003	
Fat mass[a,b]				
Decile 1	284	1 (ref)	1 (ref)	1 (ref)
Decile 2	251	0.84 (0.71–1.00)	0.91 (0.77–1.08)	0.93 (0.78–1.12)
Decile 3	267	0.86 (0.73–1.02)	0.93 (0.79–1.10)	0.97 (0.80–1.17)
Decile 4	248	0.77 (0.65–0.91)	0.84 (0.71–1.00)	0.88 (0.72–1.08)
Decile 5	252	0.76 (0.64–0.90)	0.86 (0.72–1.02)	0.91 (0.74–1.13)
Decile 6	290	0.87 (0.74–1.02)	0.96 (0.82–1.14)	1.03 (0.83–1.28)
Decile 7	264	0.78 (0.66–0.92)	0.86 (0.73–1.02)	0.95 (0.75–1.20)
Decile 8	278	0.81 (0.69–0.96)	0.90 (0.76–1.06)	1.06 (0.83–1.35)
Decile 9	274	0.80 (0.68–0.95)	0.92 (0.77–1.09)	1.14 (0.88–1.48)
Decile 10	207	0.65 (0.54–0.78)	0.75 (0.62–0.90)	0.98 (0.72–1.35)
P-trend		<.001	0.007	0.97
Lean body mass[a,c]				
Decile 1	370	1 (ref)	1 (ref)	1 (ref)
Decile 2	283	0.81 (0.69–0.94)	0.91 (0.78–1.07)	0.94 (0.79–1.11)
Decile 3	274	0.79 (0.68–0.93)	0.93 (0.79–1.09)	0.97 (0.81–1.16)
Decile 4	255	0.75 (0.64–0.88)	0.89 (0.76–1.05)	0.93 (0.76–1.12)
Decile 5	266	0.77 (0.66–0.91)	0.92 (0.79–1.08)	0.94 (0.77–1.15)
Decile 6	270	0.79 (0.68–0.92)	0.95 (0.81–1.11)	0.95 (0.77–1.17)
Decile 7	266	0.78 (0.66–0.91)	0.95 (0.81–1.12)	0.93 (0.75–1.16)
Decile 8	221	0.65 (0.55–0.76)	0.80 (0.67–0.94)	0.75 (0.59–0.95)
Decile 9	230	0.68 (0.58–0.81)	0.87 (0.73–1.03)	0.79 (0.61–1.02)
Decile 10	180	0.57 (0.48–0.69)	0.75 (0.63–0.90)	0.73 (0.53–1.00)
P-trend		<.001	0.002	0.03

Age-adjusted model included age (age stratified Cox proportional hazard model). MV model additionally adjusted for smoking status (never, past, or current smokers), time since quit smoking (< 3, 3–5.9, 6–9.9, 10–14.9, 15–19.9, > 20 years, or unknown) and cigarettes per day (1–4, 5–14, 15–24, 25–34, 35–44, 45+ cigarettes/day, or unknown), race (White or non-White), alcohol (0, 0.1–4.9, 5–9.9, 10–14.9, or 15.0+ g/day), physical activity (< 3, 3–8.9, 9–17.9, 18–26.9, or > 27 MET-hour/week), diet quality (quintiles). MV+ FM/LBM model additionally mutually adjusted for fat mass and lean body mass (deciles)

BMI body mass index, *MV* multivariable, *FM* fat mass, *LBM* lean body mass, *CI* confidence interval

[a]Derived from validated anthropometric prediction equations

[b]Height (continuous) was adjusted in the model

[c]Height was adjusted by regressing out variations due to height

and women separately was observed in participants who had high BMI and low WC (Supplementary Table S6). The highest risk of lung cancer was observed in those who had low BMI and high WC (aHR = 1.21, 95% CI 1.00–1.46). The interaction between WC and BMI was not statistically significant ($P = 0.27$).

Table 3 Association of body mass index, fat mass and lean body mass with risk of lung cancer by histological types (Pooled results of the Nurses' Health Study, 1986–2014 and the Health Professionals Follow-up Study, 1987–2012)

	Hazard Ratio (95% CI)		
	Adenocarcinoma	Squamous	Small
No. of cases	1001	363	322
BMI			
Decile 1	1 (ref)	1 (ref)	1 (ref)
Decile 2	0.99 (0.77–1.29)	0.77 (0.49–1.22)	1.01 (0.59–1.72)
Decile 3	0.96 (0.74–1.25)	1.06 (0.70–1.62)	1.32 (0.80–2.18)
Decile 4	0.87 (0.66–1.14)	0.87 (0.55–1.38)	1.35 (0.81–2.25)
Decile 5	0.90 (0.69–1.17)	1.04 (0.68–1.60)	1.35 (0.82–2.24)
Decile 6	0.85 (0.65–1.11)	1.11 (0.73–1.68)	1.54 (0.95–2.51)
Decile 7	0.93 (0.72–1.21)	0.90 (0.58–1.40)	1.62 (1.00–2.63)
Decile 8	0.77 (0.58–1.01)	0.79 (0.50–1.25)	0.86 (0.49–1.51)
Decile 9	0.88 (0.68–1.16)	0.94 (0.60–1.47)	1.74 (1.08–2.82)
Decile 10	0.62 (0.46–0.85)	0.71 (0.43–1.18)	1.48 (0.88–2.48)
P-trend	<.001	0.29	0.09
Fat mass[a,b]			
Decile 1	1 (ref)	1 (ref)	1 (ref)
Decile 2	0.98 (0.73–1.30)	1.06 (0.66–1.71)	1.48 (0.84–2.63)
Decile 3	1.12 (0.82–1.51)	0.86 (0.51–1.47)	1.18 (0.64–2.20)
Decile 4	1.07 (0.77–1.48)	0.89 (0.51–1.57)	1.17 (0.61–2.26)
Decile 5	0.92 (0.65–1.32)	1.15 (0.65–2.04)	1.25 (0.63–2.46)
Decile 6	1.05 (0.72–1.51)	1.38 (0.77–2.48)	1.46 (0.73–2.94)
Decile 7	0.84 (0.56–1.25)	1.18 (0.63–2.22)	2.39 (1.19–4.82)
Decile 8	0.94 (0.61–1.43)	1.51 (0.79–2.89)	1.88 (0.89–3.98)
Decile 9	1.17 (0.74–1.85)	1.20 (0.58–2.50)	1.75 (0.78–3.97)
Decile 10	0.88 (0.50–1.56)	1.22 (0.50–2.97)	1.13 (0.43–2.97)
P-trend	0.38	0.34	0.99
Lean body mass[a,c]			
Decile 1	1 (ref)	1 (ref)	1 (ref)
Decile 2	0.99 (0.76–1.29)	0.87 (0.55–1.36)	0.82 (0.48–1.43)
Decile 3	0.87 (0.65–1.17)	1.03 (0.64–1.66)	1.47 (0.87–2.49)
Decile 4	0.76 (0.55–1.06)	0.82 (0.49–1.39)	1.22 (0.69–2.17)
Decile 5	0.85 (0.61–1.20)	0.88 (0.51–1.50)	1.25 (0.69–2.28)
Decile 6	1.07 (0.75–1.51)	0.90 (0.52–1.57)	0.76 (0.40–1.48)
Decile 7	0.91 (0.63–1.33)	0.72 (0.40–1.31)	1.06 (0.55–2.03)
Decile 8	0.76 (0.50–1.14)	0.55 (0.29–1.07)	0.65 (0.31–1.36)
Decile 9	0.79 (0.50–1.24)	0.65 (0.32–1.33)	0.90 (0.41–1.95)
Decile 10	0.65 (0.37–1.15)	0.60 (0.25–1.44)	1.61 (0.66–3.92)
P-trend	0.21	0.18	0.56

All models were adjusted for age, smoking status (never, past, or current smokers), time since quit smoking (<3, 3–5.9, 6–9.9, 10–14.9, 15–19.9, >20 years, or unknown), cigarettes per day (1–4, 5–14, 15–24, 25–34, 35–44, 45+ cigarettes/day, or unknown), race (White or non-White), alcohol (0, 0.1–4.9, 5–9.9, 10–14.9, or 15.0+ g/day), physical activity (<3, 3–8.9, 9–17.9, 18–26.9, or >27 MET-hour/week), diet quality (quintiles). For FM and LBM models, FM and LBM were mutually adjusted (deciles)

[a]Derived from validated anthropometric prediction equations

[b]Height (continuous) was adjusted in the model

[c]Height was adjusted by regressing out variations due to height

Discussion

This study examined the association of BMI and body composition with lung cancer risk using the two large US prospective cohort studies. We found an inverse association of BMI and predicted LBM with lung cancer risk. These inverse associations were more robust in women than in men, possibly due to larger numbers. Furthermore, compared with never smokers, this inverse association of BMI and predicted LBM with lung cancer risk was more prominent among current smokers and past smokers who had smoked in previous 10 years.

Our findings are consistent with previous cohort studies that have reported an inverse association between BMI and lung cancer risk [2, 4, 5, 7, 10, 11]. A meta-analysis including 26 cohort studies showed that a 5 kg/m^2 increase in BMI corresponded to a 3.3% decrease in the risk of lung cancer indicating a nonlinear dose–response relationship [22]. Because smoking is a strong confounder in the relationship between BMI and lung cancer risk, most studies conducted the stratified analysis by smoking status and the inverse association between BMI and lung cancer risk was attenuated in non-smokers compared to that in former and current smokers [22, 23]. Although residual confounding caused by smoking has been the primary concern related to reverse causality, these associations persisted in sensitivity analysis after excluding cases within first 3–10 years, suggesting potential biological mechanisms such as a protective effect of some component of BMI against lung carcinogenesis [2, 4, 7, 10, 11]. Moreover, a meta-analysis restricted to never smokers also showed an inverse linear dose–response relationship between BMI and lung cancer risk with the relative risk of 0.89 (95% CI: 0.84–0.95) per 5 kg/m^2 increment in BMI, especially among women [24].

In contrast to BMI, central obesity indicated by WC and WHR was positively associated with risk of lung cancer regardless of sex and smoking status in previous studies [10, 25]. When we considered the joint association of BMI and WC with lung cancer risk, the highest risk was observed in low BMI and high WC, which is consistent with the results in a recent large study [10]. Among participants with high BMI, high WC was a significant risk factor in men but not women. Moreover, lowest risk was observed in those with high BMI and low WC. BMI reflects both FM and LBM, whereas WC reflects largely FM, especially central adiposity. In the joint analysis, those with high BMI and low WC have relatively high LBM and low FM, whereas those with low BMI and high WC have low LBM and high FM. Thus, the joint analysis results are compatible with a detrimental effect of low LBM but not of low FM.

Our study provides new insights for the so-called "obesity paradox" in lung cancer development. In our study,

Table 4 Association of body mass index, fat mass and lean body mass with risk of lung cancer by smoking status and time since quitting smoking (Pooled results of the Nurses' Health Study, 1986–2014 and the Health Professionals Follow-up Study, 1987–2012)

Analysis	Hazard ratio (95% CI)				
	Never-smokers	Past-smokers	Current-smokers	Never or quit smoking at least 10 years	Current or smoked in the last 10 years
No of cases					
BMI	313	1407	895	1196	1419
Decile 1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Decile 2	0.99 (0.56–1.75)	0.86 (0.68–1.09)	0.82 (0.64–1.06)	1.01 (0.76–1.33)	0.78 (0.64–0.97)
Decile 3	1.82 (1.11–2.99)	0.96 (0.76–1.20)	0.80 (0.61–1.04)	1.19 (0.91–1.55)	0.87 (0.71–1.07)
Decile 4	1.59 (0.95–2.67)	0.84 (0.66–1.07)	0.72 (0.54–0.95)	1.12 (0.85–1.47)	0.71 (0.56–0.89)
Decile 5	1.24 (0.73–2.12)	0.88 (0.70–1.11)	0.83 (0.63–1.08)	1.05 (0.80–1.37)	0.83 (0.67–1.02)
Decile 6	1.12 (0.65–1.94)	0.97 (0.77–1.21)	0.77 (0.58–1.01)	1.14 (0.88–1.48)	0.78 (0.63–0.96)
Decile 7	1.40 (0.83–2.36)	0.94 (0.75–1.17)	0.95 (0.73–1.23)	1.20 (0.93–1.56)	0.85 (0.69–1.05)
Decile 8	1.22 (0.71–2.08)	0.77 (0.60–0.97)	0.81 (0.61–1.06)	1.00 (0.77–1.31)	0.71 (0.57–0.89)
Decile 9	1.42 (0.84–2.38)	0.91 (0.72–1.14)	0.81 (0.61–1.08)	1.13 (0.87–1.48)	0.80 (0.64–0.99)
Decile 10	0.88 (0.49–1.59)	0.77 (0.60–0.98)	0.69 (0.50–0.95)	0.86 (0.65–1.15)	0.70 (0.55–0.89)
P-trend	0.38	0.03	0.09	0.24	0.003
Fat mass[a,b]					
Decile 1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Decile 2	1.41 (0.78–2.57)	0.99 (0.77–1.28)	0.80 (0.59–1.06)	1.09 (0.81–1.47)	0.87 (0.69–1.09)
Decile 3	1.87 (1.02–3.42)	0.88 (0.67–1.16)	0.96 (0.71–1.29)	1.11 (0.81–1.51)	0.92 (0.73–1.18)
Decile 4	1.55 (0.81–2.95)	0.82 (0.62–1.10)	0.87 (0.62–1.21)	0.97 (0.70–1.35)	0.87 (0.66–1.13)
Decile 5	1.34 (0.68–2.66)	0.95 (0.71–1.27)	0.81 (0.56–1.15)	1.09 (0.78–1.52)	0.81 (0.61–1.08)
Decile 6	1.51 (0.75–3.04)	1.01 (0.75–1.36)	1.00 (0.69–1.44)	1.12 (0.80–1.58)	1.01 (0.76–1.34)
Decile 7	1.28 (0.61–2.72)	0.93 (0.68–1.27)	0.97 (0.66–1.42)	1.02 (0.71–1.47)	0.94 (0.69–1.27)
Decile 8	1.56 (0.71–3.40)	0.96 (0.69–1.34)	1.15 (0.77–1.72)	1.16 (0.80–1.69)	1.01 (0.73–1.39)
Decile 9	1.35 (0.57–3.21)	1.04 (0.73–1.49)	1.39 (0.90–2.16)	1.20 (0.80–1.81)	1.14 (0.80–1.61)
Decile 10	1.11 (0.39–3.21)	1.03 (0.67–1.58)	0.91 (0.52–1.59)	0.86 (0.53–1.42)	1.13 (0.75–1.72)
P-trend	0.63	0.98	0.61	0.72	0.75
Lean body mass[a,c]					
Decile 1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Decile 2	0.93 (0.55–1.56)	0.94 (0.74–1.19)	0.93 (0.71–1.21)	1.07 (0.82–1.40)	0.87 (0.70–1.08)
Decile 3	0.83 (0.48–1.46)	1.09 (0.85–1.40)	0.85 (0.63–1.15)	1.09 (0.82–1.44)	0.92 (0.73–1.16)
Decile 4	1.04 (0.59–1.83)	0.95 (0.73–1.25)	0.84 (0.61–1.16)	1.14 (0.85–1.53)	0.81 (0.62–1.04)
Decile 5	0.89 (0.48–1.65)	0.96 (0.73–1.26)	0.91 (0.65–1.28)	1.03 (0.75–1.41)	0.91 (0.70–1.18)
Decile 6	0.94 (0.50–1.80)	0.98 (0.74–1.31)	0.91 (0.64–1.29)	1.20 (0.87–1.65)	0.81 (0.61–1.07)
Decile 7	1.28 (0.67–2.44)	0.94 (0.69–1.26)	0.82 (0.56–1.20)	1.13 (0.81–1.58)	0.82 (0.61–1.10)
Decile 8	0.80 (0.38–1.66)	0.79 (0.57–1.09)	0.68 (0.45–1.02)	0.83 (0.57–1.20)	0.72 (0.52–0.99)
Decile 9	0.90 (0.40–2.00)	0.84 (0.59–1.18)	0.68 (0.43–1.05)	0.97 (0.66–1.44)	0.70 (0.49–0.98)
Decile 10	1.00 (0.37–2.71)	0.77 (0.51–1.17)	0.60 (0.35–1.04)	1.09 (0.68–1.76)	0.55 (0.36–0.84)
P-trend	0.95	0.21	0.04	0.93	0.008

All models were adjusted for age, smoking status (never, past, or current smokers), time since quit smoking (< 3, 3–5.9, 6–9.9, 10–14.9, 15–19.9, > 20 years, or unknown), cigarettes per day (1–4, 5–14, 15–24, 25–34, 35–44, 45+ cigarettes/day, or unknown), race (White or non-White), alcohol (0, 0.1–4.9, 5–9.9, 10–14.9, or 15.0+ g/day), physical activity (< 3, 3–8.9, 9–17.9, 18–26.9, or > 27 MET-hour/week), diet quality (quintiles). For FM and LBM models, FM and LBM were mutually adjusted (deciles)

the low LBM rather than low FM was associated with the increased risk of lung cancer in low BMI range. Moreover, 45% lower risk of lung cancer was observed in those in the highest decile of LBM compared to those in the lowest decile among those who were current smokers or had smoked in the last 10 years. Possibly, low lean body and muscle mass in smokers may reflect individuals' enhanced susceptibility to smoking related carcinogenesis [26]. Smoking generally has negative effects on muscle mass by impairing muscle protein synthesis process [27]

and inducing oxidative stress [28]. Men with low BMI showed higher oxidative DNA damage related to smoking [29]. Moreover, participants in the lowest BMI decile could be heavier smokers than those in other deciles, and may mirror the strong dose–response relationship between smoking and lung cancer [30].

The role of adiposity on lung cancer risk has been controversial. The term "obesity paradox" implies that adiposity itself confers some benefit on lung cancer risk. For example, it has been suggested that fat tissue might act as potential buffer to dilute toxic substances or store fat-soluble antioxidants [31]. However, our results suggest that low BMI is associated with higher risk because of its reflection of low lean mass, not higher FM. Because of the strong effect of smoking on body composition and of smoking on lung cancer risk, interpreting BMI as a marker of adiposity on lung cancer risk is problematic. In fact, Mendelian randomization studies, less prone to confounding, suggest that genetically high BMI is associated with a higher risk of lung cancer [32]. In our study, men in high predicted FM deciles had high risk of lung cancer, especially in never smokers. Sex differential fat distribution might cause high risk of lung cancer among men with high FM, which is typically intra-abdominal fat in men compared to hip or thigh fat distribution in women [33]. Possibly, metabolic disorders related to visceral fat accumulation might increase the risk of lung cancer through certain adipocytokines such as leptin and lower adiponectin [34].

Lastly, the inverse association between BMI, FM and LBM and risk of lung cancer could result from a sequence of smoking-related lung disease. People affected by smoking-related chronic disease (e.g., COPD) tend to have sarcopenic features with low LBM but also some degree of low FM due to elevated resting energy expenditure [35]. Moreover, those with chronic lung inflammation might have a high risk of lung cancer via mechanisms involving cell death and hyperplasia of airway epithelial cells [36].

We investigated differential association of BMI, FM and LBM with the histological lung cancer types considering of different etiology. Consistent with previous studies, adenocarcinoma, which is less influenced by smoking [37] had statistically significant inverse association with BMI among histological types, irrespective of smoking status [2, 7].

The current study has several limitations to be considered. First, we used predicted FM and LBM instead of actual measurement, which may result in measurement errors. However, the previous large validation study showed high predictive ability of anthropometric equations (R^2 of 0.90 and higher), and thus results based on direct DXA would likely show similar relationships between FM and LBM and lung cancer risk. Supporting this, the predicted FM was equally predictive of obesity-related biomarkers as DXA measured FM [17]. Considering low availability of DXA in large epidemiologic settings, anthropometric prediction equations could be useful to estimate FM and LBM. Moreover, the patterns observed in the joint analysis of BMI and WC are compatible with expectations based on how combinations of BMI and WC relate to FM and LBM. Second, we used self-reported weight and height to calculate the predicted FM and LBM. However, a previous internal validation study showed that correlation between self-reported weight and technician measured weight was 0.97 for men and 0.97 for women, which can have minimal effect on epidemiologic studies [38]. Third, we cannot rule out reverse causality between thinness and high lung cancer risk [39]. This inverse association could have arisen from undiagnosed lung cancer during the follow up. However, the analyses with 4–12 year lag times showed a consistent association, which minimize the possibility of the reverse causality. Fourth, participants were largely restricted to White health professionals, which may not be applied to other groups. But there is no evidence that the overall biologic features of smoking, anthropometric factors and lung cancer risk would be qualitatively different in relation to lung cancer risk from other occupation and ethnic groups.

In summary, BMI was inversely associated with risk of lung cancer, particularly among current smokers or former smokers. Predicted LBM rather than predicted FM accounted for the inverse association of BMI with lung cancer risk. Even though the definite reasons underlying this association are uncertain, low LBM by smoking may reflect more susceptibility to smoking-related carcinogenicity.

Acknowledgment We would like to thank the participants and staff of the NHS and HPFS for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data.

Author contributions DHL and ELG contributed to the study design and conception. S-MJ, DHL and ELG drafted the manuscript and the tables. DHL and ELG contributed to the data acquisition and analysis. DHL contributed to the statistical analysis. S-MJ, DHL and ELG critically revised the manuscript. All authors read and approved the final manuscript.

Funding This work was supported by the National Institutes of Health (UM1 CA167552, R01 HL35464, UM1 CA186107, P01 CA87969, and R03 CA223619).

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569–78. https://doi.org/10.1016/s0140-6736(08)60269-x.
2. Smith L, Brinton LA, Spitz MR, Lam TK, Park Y, Hollenbeck AR, et al. Body mass index and risk of lung cancer among never, former, and current smokers. J Natl Cancer Inst. 2012;104(10):778–89. https://doi.org/10.1093/jnci/djs179.
3. Sanikini H, Yuan J-M, Butler LM, Koh W-P, Gao Y-T, Steffen A, et al. Body mass index and lung cancer risk: a pooled analysis based on nested case-control studies from four cohort studies. BMC Cancer. 2018;18(1):220. https://doi.org/10.1186/s12885-018-4124-0.
4. Kabat GC, Kim M, Hunt JR, Chlebowski RT, Rohan TE. Body mass index and waist circumference in relation to lung cancer risk in the Women's Health Initiative. Am J Epidemiol. 2008;168(2):158–69. https://doi.org/10.1093/aje/kwn109.
5. Bethea TN, Rosenberg L, Charlot M, O'Connor GT, Adams-Campbell LL, Palmer JR. Obesity in relation to lung cancer incidence in African American women. Cancer Causes Control. 2013;24(9):1695–703. https://doi.org/10.1007/s10552-013-0245-6.
6. El-Zein M, Parent ME, Nicolau B, Koushik A, Siemiatycki J, Rousseau MC. Body mass index, lifetime smoking intensity and lung cancer risk. Int J Cancer. 2013;133(7):1721–31. https://doi.org/10.1002/ijc.28185.
7. Olson JE, Yang P, Schmitz K, Vierkant RA, Cerhan JR, Sellers TA. Differential association of body mass index and fat distribution with three major histologic types of lung cancer: evidence from a cohort of older women. Am J Epidemiol. 2002;156(7):606–15. https://doi.org/10.1093/aje/kwf084.
8. Chiolero A, Faeh D, Paccaud F, Cornuz J. Consequences of smoking for body weight, body fat distribution, and insulin resistance. Am J Clin Nutr. 2008;87(4):801–9. https://doi.org/10.1093/ajcn/87.4.801.
9. Malhotra J, Malvezzi M, Negri E, La Vecchia C, Boffetta P. Risk factors for lung cancer worldwide. Eur Respir J. 2016;48(3):889–902. https://doi.org/10.1183/13993003.00359-2016.
10. Yu D, Zheng W, Johansson M, Lan Q, Park Y, White E, et al. Overall and central obesity and risk of lung cancer: a pooled analysis. J Natl Cancer Inst. 2018;110(8):831–42. https://doi.org/10.1093/jnci/djx286.
11. Dewi NU, Boshuizen HC, Johansson M, Vineis P, Kampman E, Steffen A, et al. Anthropometry and the Risk of Lung Cancer in EPIC. Am J Epidemiol. 2016;184(2):129–39. https://doi.org/10.1093/aje/kwv298.
12. Padwal R, Leslie WD, Lix LM, Majumdar SR. Relationship among body fat percentage, body mass index, and all-cause mortality: a cohort study. Ann Intern Med. 2016;164(8):532–41. https://doi.org/10.7326/m15-1181.
13. Han SS, Kim KW, Kim KI, Na KY, Chae DW, Kim S, et al. Lean mass index: a better predictor of mortality than body mass index in elderly Asians. J Am Geriatr Soc. 2010;58(2):312–7. https://doi.org/10.1111/j.1532-5415.2009.02672.x.
14. Lee DH, Giovannucci EL. Body composition and mortality in the general population: a review of epidemiologic studies. Exp Biol Med. 2018;243(17–18):1275–85. https://doi.org/10.1177/1535370218818161.
15. Tsai S. Importance of lean body mass in the oncologic patient. Nutr Clin Pract. 2012;27(5):593–8. https://doi.org/10.1177/0884533612457949.
16. Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutr. 2005;82(1):53–9. https://doi.org/10.1093/ajcn.82.1.53.
17. Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Sun Q, et al. Development and validation of anthropometric prediction equations for lean body mass, fat mass and percent fat in adults using the National Health and Nutrition Examination Survey (NHANES) 1999–2006. Br J Nutr. 2017;118(10):858–66. https://doi.org/10.1017/s0007114517002665.
18. Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Willett WC, et al. Comparison of the association of predicted fat mass, body mass index, and other obesity indicators with type 2 diabetes risk: two large prospective studies in US men and women. Eur J Epidemiol. 2018;33(11):1113–23. https://doi.org/10.1007/s10654-018-0433-5.
19. Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Willett WC, et al. Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: prospective US cohort study. BMJ. 2018;362:k2575. https://doi.org/10.1136/bmj.k2575.
20. Hanyuda A, Lee DH, Ogino S, Wu K, Giovannucci EL. Long-term status of predicted body fat percentage, body mass index, and other anthropometric factors with risk of colorectal carcinoma: Two large prospective cohort studies in the US. Int J Cancer. 2019.
21. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National death index and Equifax nationwide death search. Am J Epidemiol. 1994;140(11):1016–9. https://doi.org/10.1093/oxfordjournals.aje.a117191.
22. Duan P, Hu C, Quan C, Yi X, Zhou W, Yuan M, et al. Body mass index and risk of lung cancer: systematic review and dose-response meta-analysis. Sci Rep. 2015;5:16938. https://doi.org/10.1038/srep16938.
23. Yang Y, Dong J, Sun K, Zhao L, Zhao F, Wang L, et al. Obesity and incidence of lung cancer: a meta-analysis. Int J Cancer. 2013;132(5):1162–9. https://doi.org/10.1002/ijc.27719.
24. Zhu H, Zhang S. Body mass index and lung cancer risk in never smokers: a meta-analysis. BMC Cancer. 2018;18(1):635. https://doi.org/10.1186/s12885-018-4543-y.
25. Lam TK, Moore SC, Brinton LA, Smith L, Hollenbeck AR, Gierach GL, et al. Anthropometric measures and physical activity and the risk of lung cancer in never-smokers: a prospective cohort study. PLoS ONE. 2013;8(8):e70672. https://doi.org/10.1371/journal.pone.0070672.
26. Kark JD, Yaari S, Rasooly I, Goldbourt U. Are lean smokers at increased risk of lung cancer? The Israel Civil Servant Cancer Study. Arch Intern Med. 1995;155(22):2409–16.
27. Petersen AMW, Magkos F, Atherton P, Selby A, Smith K, Rennie MJ, et al. Smoking impairs muscle protein synthesis and increases the expression of myostatin and MAFbx in muscle. Am J Physiol Endocrinol Metab. 2007;293(3):E843–8. https://doi.org/10.1152/ajpendo.00301.2007.
28. Rom O, Kaisari S, Aizenbud D, Reznick AZ. Sarcopenia and smoking: a possible cellular model of cigarette smoke effects on muscle protein breakdown. Ann N Y Acad Sci. 2012;1259(1):47–53. https://doi.org/10.1111/j.1749-6632.2012.06532.x.
29. Mizoue T, Kasai H, Kubo T, Tokunaga S. Leanness, smoking, and enhanced oxidative DNA damage. Cancer Epidemiol Biomark Prev. 2006;15(3):582–5. https://doi.org/10.1158/1055-9965.epi-05-0658.
30. Flanders WD, Lally CA, Zhu B-P, Henley SJ, Thun MJ. Lung cancer mortality in relation to age, duration of smoking, and daily cigarette consumption. Results from Cancer Prevention Study II. Cancer Res. 2003;63(19):6556–62.
31. Zhang X, Liu Y, Shao H, Zheng X. Obesity paradox in lung cancer prognosis: evolving biological insights and clinical implications.

J Thorac Oncol. 2017;12(10):1478–88. https://doi.org/10.1016/j.jtho.2017.07.022.
32. Carreras-Torres R, Johansson M, Haycock PC, Wade KH, Relton CL, Martin RM, et al. Obesity, metabolic factors and risk of different histological types of lung cancer: a Mendelian randomization study. PLoS ONE. 2017;12(6):e0177875. https://doi.org/10.1371/journal.pone.0177875.
33. Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues—the biology of pear shape. Biol Sex Differ. 2012;3(1):13. https://doi.org/10.1186/2042-6410-3-13.
34. Ntikoudi E, Kiagia M, Boura P, Syrigos KN. Hormones of adipose tissue and their biologic role in lung cancer. Cancer Treat Rev. 2014;40(1):22–30. https://doi.org/10.1016/j.ctrv.2013.06.005.
35. Creutzberg EC, Schols AM, Bothmer-Quaedvlieg FC, Wouters EF. Prevalence of an elevated resting energy expenditure in patients with chronic obstructive pulmonary disease in relation to body composition and lung function. Eur J Clin Nutr. 1998;52(6):396–401.
36. Goldkorn T, Filosto S. Lung injury and cancer: mechanistic insights into ceramide and EGFR signaling under cigarette smoke. Am J Respir Cell Mol Biol. 2010;43(3):259–68. https://doi.org/10.1165/rcmb.2010-0220RT.
37. Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. Lung Cancer. 2001;31(2–3):139–48.
38. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology. 1990;1(6):466–73. https://doi.org/10.1097/00001648-199011000-00009.
39. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. Am J Clin Nutr. 2010;91(4):1133s–7s. https://doi.org/10.3945/ajcn.2010.28608C.