American Journal of Epidemiology

Vol. 184, No. 2
DOI: 10.1093/aje/kwv298
Advance Access publication:
July 1, 2016

Original Contribution

Anthropometry and the Risk of Lung Cancer in EPIC

Nikmah Utami Dewi, Hendriek C. Boshuizen*, Mattias Johansson, Paolo Vineis, Ellen Kampman, Annika Steffen, Anne Tjønneland, Jytte Halkjær, Kim Overvad, Gianluca Severi, Guy Fagherazzi, Marie-Christine Boutron-Ruault, Rudolf Kaaks, Kuanrong Li, Heiner Boeing, Antonia Trichopoulou, Christina Bamia, Eleni Klinaki, Rosario Tumino, Domenico Palli, Amalia Mattiello, Giovanna Tagliabue, Petra H. Peeters, Roel Vermeulen, Elisabete Weiderpass, Inger Torhild Gram, José María Huerta, Antonio Agudo, María-José Sánchez, Eva Ardanaz, Miren Dorronsoro, José Ramón Quirós, Emily Sonestedt, Mikael Johansson, Kjell Grankvist, Tim Key, Kay-Tee Khaw, Nick Wareham, Amanda J. Cross, Teresa Norat, Elio Riboli, Anouar Fanidi, David Muller, and H. Bas Bueno-de-Mesquita

* Correspondence to Dr. Hendriek C. Boshuizen, Department of Statistics, Informatics and Mathematical Modelling (SIM), National Institute of Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, the Netherlands (e-mail:Hendriek.boshuizen@rivm.nl).

Initially submitted May 8, 2015; accepted for publication October 22, 2015.

The associations of body mass index (BMI) and other anthropometric measurements with lung cancer were examined in 348,108 participants in the European Investigation Into Cancer and Nutrition (EPIC) between 1992 and 2010. The study population included 2,400 case patients with incident lung cancer, and the average length of follow-up was 11 years. Hazard ratios were calculated using Cox proportional hazard models in which we modeled smoking variables with cubic splines. Overall, there was a significant inverse association between BMI (weight (kg)/height $(m)^2$) and the risk of lung cancer after adjustment for smoking and other confounders (for BMI of 30.0–34.9 versus 18.5–25.0, hazard ratio = 0.72, 95% confidence interval: 0.62, 0.84). The strength of the association declined with increasing follow-up time. Conversely, after adjustment for BMI, waist circumference and waist-to-height ratio were significantly positively associated with lung cancer risk (for the highest category of waist circumference vs. the lowest, hazard ratio = 1.25, 95% confidence interval: 1.05, 1.50). Given the decline of the inverse association between BMI and lung cancer over time, the association is likely at least partly due to weight loss resulting from preclinical lung cancer that was present at baseline. Residual confounding by smoking could also have influenced our findings.

body mass index; lung cancer; obesity; smoking; waist circumference; waist to hip ratio; waist-to-height ratio

Abbreviations: BMI, body mass index; EPIC, European Prospective Investigation Into Cancer and Nutrition; WC, waist circumference; WHR, waist to hip ratio; WHtR, waist to height ratio.

Body mass index (BMI) was found to be inversely related to the risk of lung cancer in 3 meta-analyses, 2 of which included only cohort studies on the incidence of lung cancer (1, 2) (1 included only males) and 1 of which also included case-control studies and studies on lung cancer mortality (3). This relationship was also found in 2 cohort studies on lung cancer incidence that were not included in these meta-analyses (4, 5). A higher risk of lung cancer in persons with lower BMIs might be explained by preclinical lung cancer leading to weight loss before diagnosis or by uncontrolled or residual confounding by smoking, which influences both BMI and lung cancer (6). Evidence of the role of confounding by smoking can be obtained by stratifying the analyses for smoking, because doing so should cause the association due to confounding to disappear in never smokers. Because lung cancer is relatively rare in never smokers, here evidence is less consistent. Most studies show nonsignificant relationships in never smokers, but often the power to detect such a relationship is limited. In 1 meta-analysis (which included

case-control studies), investigators found an inverse association in never smokers, although it was less strong than that in former and current smokers (3). In another meta-analysis in which the researchers applied more rigorous exclusion criteria, there was no evidence of such a relationship (1). Recently, Renehan et al. (7) conducted a simulation study and showed that a modest correlation of −0.10 between BMI and the number of cigarettes smoked might explain the observed inverse association in smokers found in the article by Smith et al. (8) through residual confounding.

In addition to BMI, which is a measure of general obesity, fat distribution might play a role in the development of lung cancer (6, 9, 10). Abdominal adiposity is reflected by a higher waist-to-hip ratio (WHR) and a higher waist circumference (WC) relative to other persons with the same BMI (11, 12). Another measure of abdominal adiposity is waist-to-height ratio (WHtR) (13). Results from 3 cohort studies have shown a positive association between lung cancer incidence and WHR and/or WC after adjustment for BMI (6, 9, 10), and results from another have shown a positive association with mortality (14); however, to our knowledge, the association between WHtR and lung cancer risk has not been evaluated. In 1 study, investigators looked for the association between hip circumference and the risk of lung cancer in never smokers and found an inverse association after adjustment for BMI (9).

Height is another anthropometric factor that has been studied with regard to risk of lung cancer in 9 cohort studies (6, 10, 15–21). In most studies, no associations were found. However, in 2 studies, researchers found a positive association between height and lung cancer in subgroups of the population; one was a study of women who had never smoked (6), and the other was a study of men who had never smoked (20).

In the present study, we examined the associations of the anthropometric measures BMI, height, WC, hip circumference, WHR, and WHtR with the risk of lung cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). In EPIC, available anthropometric data are mostly based on measurements rather than self-report. Detailed data on smoking were obtained, allowing thorough modeling to minimize confounding by smoking. Special attention was given to the possible role of preclinical lung cancer as an explanation for the inverse relationship of lung cancer risk with BMI by studying whether the association changes with time since BMI measurement.

METHODS

Study design

EPIC is a prospective cohort study that consists of more than 500,000 subjects recruited between 1992 and 2000. Subjects were enrolled in 23 centers in 10 European countries (France, Italy, Spain, United Kingdom, the Netherlands, Greece, Germany, Sweden, Denmark, and Norway) (22). Most centers sampled from the general population, with participant ages ranging mostly between 30 and 70 years. The study investigators obtained ethical approval from participating centers and the International Agency for Research on Cancer ethics committees. Informed consent was given by all study participants (23).

Study population

In the present study, we used data from 348,108 subjects. We excluded participants with prevalent cancer (except nonmelanoma skin cancer) ($n = 23,785$); participants with only uncalibrated self-reported baseline information (all of the Norwegian cohort, most of the French cohort); participants with missing information on smoking ($n = 11,746$), weight ($n = 92,010$), height ($n = 91,342$), WC ($n = 118,933$), hip circumference ($n = 121,790$), baseline educational level ($n = 8,055$), physical activity level ($n = 44,664$), current pregnancy ($n = 26,804$), or diet ($n = 6,193$); and participants within the extreme percentiles of the ratio of energy intake to estimated energy requirement ($n = 15,854$). Excluded participants were counted in multiple groups.

Assessment of anthropometric data, lifestyle factors, and diet

Anthropometric measurements, including weight, height, WC, and hip circumference, were obtained using a standard protocol (22). In the present study, we also used self-reported information from the health-conscious cohort from the EPIC-Oxford Study that was calibrated using a predictive equation based on data from the general population of the EPIC-Oxford Study cohort (24).

BMI was calculated as weight in kilograms divided by square of height in meters; WHR was calculated at as waist circumference in centimeters divided by hip circumference in centimeters; and WHtR was calculated as height in centimeters divided by waist circumference in centimeters. Country-specific validated food frequency questionnaires were used to measure usual dietary habits. Other characteristics were assessed using standardized questionnaires (23).

Assessment of endpoints

Data on lung cancer were obtained from cancer registries (Italy, Spain, United Kingdom, the Netherlands, Sweden, Denmark, and Norway) or by using a combination of health insurance data, cancer and pathology registry data, and information from closest family members (France, Greece, and Germany) (23). Follow-up time ended at diagnosis of a first primary cancer, death, migration, last known contact, or end of follow-up (ranging from 2004 to 2010, depending on the center), whichever came first.

Based on the *International Classification of Disease for Oncology, Second Edition*, lung cancer was defined as all invasive cancers coded with C34. Lung cancers were classified into 5 histological categories according to the World Health Organization's International Histological Classification of Tumours: squamous-cell carcinoma (codes 8070, 8071, 8072, 8073, 8075, 8083, 8094, and 8123), small-cell carcinoma (codes 8041, 8042, 8043, 8044, 8045, and 8246), large-cell carcinoma (codes 8012, 8020, and 8021), and adenocarcinoma (codes 8140, 8200, 8211, 8230, 8250, 8251, 8253, 8260, 8310, 8470, 8480, 8481, 8490, and 8550), with other histological types (codes 8000, 8001, 8003, 8010, 8011, 8022, 8030, 8031, 8032, 8046, 8240, 8560, 8710, 8800, 8801, 8990, 9120, 9133, and 9699) were assigned to "unclassified."

Statistical analysis

Because smoking is an important confounder, we present standardized mean values of the anthropometric variables by smoking status. Standardization (using least square means from linear regression) was used because crude means are heavily confounded, for example, by center and age. As a standard, we used the population mean value for continuous variables and population marginal proportions for the categorical variables.

Cox proportional hazard models with age as the underlying time variable were used to analyze the associations between anthropometric measures and the risk of lung cancer (25). For BMI, WC, and WHR, World Health Organization categorizations were used (11). BMI was categorized as <18.5, 18.5–24.9, 25.0–29.9; 30.0–34.9, or ≥35.0. WC was categorized as <94.0, 94.0–101.9, and ≥102.0 cm for men and <80.0, 80.0–87.9, and ≥88.0 cm for women, and WHR was categorized <0.950, 0.950–0.999, and >1.00 for men and <0.800, 0.800–0.849, and >0.850 for women. For WHtR, hip circumference, and height, categories were based on sex-specific study-wide quartiles, with the lowest quartile serving as the reference category. To test for trend, we assigned each participant the median value of the category to which they belonged and used this variable as a continuous variable. This "trend variable" was also used to test for interactions with smoking, sex, or time in follow-up.

All Cox models were stratified by study center, sex, and age at recruitment in 1-year categories. The stratification by age at recruitment was done in order to adjust for time in study: By matching individuals of the same age during follow-up on age of recruitment, one implicitly matches on time in follow-up. The proportional hazard assumption was tested by adding interaction terms between age (time dependent) and all covariates in the models. Only for smoking status was the proportional hazard assumption not satisfied. Therefore, smoking status was also included as a stratum variable in the Cox models. In addition to stratifying by smoking, we included the average number of lifetime cigarettes smoked per day, the number of cigarettes smoked per day at baseline, and the duration of cigarette smoking in years in the model as

Table 1. Hazard Ratios for the Associations of Lung Cancer With Waist Circumference, Hip Circumference, and Waist-to-Height Ratio by Sex After Additional Adjustment for Body Mass Index, European Prospective Investigation Into Cancer and Nutrition, 1992–2010

Measure and Category	No. of Cases	All Participants		Men		Women	
		HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI
Waist circumference[b]							
Normal	1,086	1.00	Referent	1.00	Referent	1.00	Referent
Increased	674	1.07	0.94, 1.22	1.15	0.96, 1.36	0.99	0.81, 1.19
Substantially increased	640	1.25	1.05, 1.50	1.26	0.98, 1.61	1.31	1.02, 1.68
P for trend		0.008		0.07		0.06	
Quartile of hip circumference[c]							
1	663	1.00	Referent	1.00	Referent	1.00	Referent
2	640	0.91	0.79, 1.05	0.95	0.79, 1.14	0.90	0.73, 1.11
3	537	0.85	0.72, 1.00	0.88	0.70, 1.10	0.87	0.69, 1.11
4	560	0.94	0.75, 1.17	1.08	0.81, 1.44	0.89	0.64, 1.24
P for trend		0.99		0.66		0.55	
Quartile of WHtR[d]							
1	568	1.00	Referent	1.00	Referent	1.00	Referent
2	681	1.02	0.86, 1.21	0.98	0.78, 1.23	1.09	0.85, 1.40
3	550	1.13	0.95, 1.35	1.15	0.90, 1.47	1.15	0.88, 1.50
4	601	1.35	1.07, 1.69	1.22	0.89, 1.67	1.59	1.14, 2.23
P for trend		0.0006		0.19		0.002	

Abbreviations: CI, confidence interval; HR, hazard ratio; WHtR, waist-to-height ratio.

[a] Calculated using Cox regression with age as the underlying time variable, stratification by center, age at recruitment, sex, and smoking status, and adjustment for the duration of smoking, the lifetime number of cigarettes smoked, the number of cigarettes smoked at baseline (all modeled with cubic spline functions), educational level, physical activity level, fruit consumption, vegetable consumption, meat consumption, fat intake, energy intake, and anthropometric variables, including body mass index.

[b] The cutoffs for normal, increased, and substantially increased were <94.0, 94.0–101.9, and ≥102.0 cm, respectively, in men and <80.0, 80.0–87.9, and ≥88.0 cm, respectively, in women.

[c] The cutoffs for quartiles 1–4 were <96.00 cm, 96.00–100.25 cm, 100.26–104.99 cm, and ≥105.00 cm, respectively, in men and <95.00 cm, 95.00–99.99 cm, 100.00–105.99 cm, and ≥106.00 cm, respectively, in women.

[d] The cutoffs for quartiles 1–4 were <0.500, 0.500–0.539, 0.540–0.579, and ≥0.580, respectively, for men and <0.440, 0.440–0.479, 0.480–0.539, and ≥0.540, respectively, for women.

restricted cubic spline functions, using 5 knots (placed at the 5th, 25th, 50th, 75th, and 95th percentiles) (26).

We included the following potential confounders based on a review of evidence from cancer-related meta-analyses (27) and an earlier EPIC study (28): highest educational level attained (none; primary school; technical, professional, or secondary school; or college/university degree), physical activity level as given by the Cambridge Physical Activity Index (inactive, moderately inactive, moderately active, or active) (29), vegetable consumption (g/day), fruit consumption (g/day), red and processed meat consumption (g/day), fat intake (g/day), total energy intake (kcal/day), and height (m). The model for height was adjusted for BMI (continuous). In additional analyses, models for WC, WtHR, and hip circumference were further adjusted for BMI. Furthermore, we conducted a priori specified subgroup analyses by smoking status and by histological type.

Lastly, in order to see the influence of preclinical disease, the analysis was conducted separately for different lengths of

Table 2. Hazard Ratio for the Associations of Lung Cancer With Body Mass Index, Waist Circumference, Waist-to-Hip Ratio, and Waist-to-Height Ratio by Smoking Status, European Prospective Investigation Into Cancer and Nutrition, 1992–2010

Measure and Category	Smoking Status						*P* for Interaction
	Never (*n* = 202)		Former (*n* = 613)		Current (*n* = 1,585)		
	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI	
BMI[b]							0.03
<18.5	0.61	0.09, 4.42	0.57	0.08, 4.20	1.59	1.07, 2.37	
18.5–24.9	1.00	Referent	1.00	Referent	1.00	Referent	
25.0–29.9	0.82	0.60, 1.13	1.04	0.83, 1.31	0.75	0.66, 0.84	
30.0–34.9	0.60	0.37, 0.98	0.91	0.67, 1.23	0.70	0.57, 0.85	
≥35.0	0.63	0.28, 1.39	1.25	0.75, 2.09	0.70	0.47, 1.03	
P for trend		0.05		0.82		<0.0001	
Waist circumference[c]							0.22
Normal	1.00	Referent	1.00	Referent	1.00	Referent	
Increased	1.21	0.83, 1.76	1.09	0.84, 1.41	1.06	0.90, 1.24	
Substantially increased	0.95	0.54, 1.65	1.15	0.80, 1.63	1.38	1.10, 1.72	
P for trend		0.96		0.42		0.005	
WHR[d]							
Normal	1.00	Referent	1.00	Referent	1.00	Referent	0.03
Moderate	1.17	0.84, 1.63	1.08	0.85, 1.38	0.94	0.81, 1.08	
High	0.76	0.0, 1.15	1.44	1.14, 1.82	0.98	0.85, 1.12	
P for trend		0.44		0.006		0.90	
Quartile of WHtR[e]							
1	1.00	Referent	1.00	Referent	1.00	Referent	0.18
2	1.03	0.60, 1.74	1.23	0.79, 1.90	1.01	0.83, 1.22	
3	1.27	0.74, 2.19	1.46	0.94, 2.27	1.07	0.86, 1.32	
4	1.31	0.66, 2.64	1.64	0.99, 2.73	1.34	1.01, 1.76	
P for trend		0.35		0.05		0.003	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; WHR, waist-to hip-ratio; WHtR, waist-to-height ratio.

[a] Calculated using Cox regression with age as the underlying time variable, stratification by center, age at recruitment, and sex, and adjustment for the duration of smoking, the lifetime number of cigarettes smoked, the number of cigarettes smoked at baseline (all modeled with cubic spline functions), educational level, physical activity level, fruit consumption, vegetable consumption, meat consumption, fat intake, energy intake, and height. For waist circumference and WHtR, models were additionally adjusted for BMI.

[b] Weight (kg)/height (m)^2.

[c] The cutoffs for normal, increased, and substantially increased were <94.0, 94.0–101.9, and ≥102.0 cm, respectively, in men and <80.0, 80.0–87.9, and ≥88.0 cm, respectively, in women.

[d] The cutoffs for normal, moderate, and high were <0.950, 0.950–0.999, and >1.00, respectively, in men and <0.800, 0.800–0.849, and >0.850, respectively, in women.

[e] The cutoffs for quartiles 1–4 were <0.500, 0.500–0.539, 0.540–0.579, and ≥0.580, respectively, for men and <0.440, 0.440–0.479, 0.480–0.539, and ≥0.540, respectively, for women.

follow-up (0–2, 3–5, 6–10, or 11–17 years). To visualize these results, we modeled time in follow-up as a restricted cubic spline that included an interaction of this spline function with BMI.

Sensitivity analyses were conducted to assess the consistency of the findings by excluding the calibrated self-reported measurements, by using only histologically confirmed lung cancer cases, or by restricting to cases detected before death. *P* values less than 0.05 (2-sided) were considered statistically significant, and analyses were performed using SAS, versions 9.2 and 9.3 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

After a mean of 11.1 years of follow-up, 2,400 incident cases of lung cancer were identified (1,362 men and 1,038 women), of which 794 were adenocarcinomas, 476 were squamous-cell carcinomas, 387 were small-cell carcinoma, 173 large-cell were carcinomas, and 570 were unclassified lung cancers. Of all cases, 86.6% were microscopically confirmed by cytology, hematology, or autopsy.

Men were more likely to be overweight and obese than were women (Web Table 1, available at http://aje.oxfordjournals.org/).

Table 3. Hazard Ratios for the Associations of Subtypes of Lung Cancer With Body Mass Index, Waist Circumference, Waist-to-Hip Ratio, and Waist-to-Height Ratio, European Prospective Investigation Into Cancer and Nutrition, 1992–2010

Measure and Category	Lung Cancer Subtype									
	Adenocarcinoma (*n* = 794)		Squamous-Cell Carcinoma (*n* = 476)		Small-Cell Carcinoma (*n* = 387)		Large-Cell Carcinoma (*n* = 173)		Unclassified (*n* = 570)	
	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI
BMI[b]										
<18.5	2.39	1.44, 3.95	0.27	0.04, 2.03	1.51	0.60, 3.83	0.81	0.10, 6.87	0.98	0.40, 2.44
18.5–24.9	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
25.0–29.9	0.72	0.60, 0.85	0.77	0.60, 0.98	1.04	0.80, 1.35	0.85	0.54, 1.34	0.83	0.68, 1.03
30.0–34.9	0.48	0.36, 0.65	0.68	0.48, 0.97	1.12	0.78, 1.61	0.68	0.34, 1.35	0.89	0.66, 1.19
≥35	0.54	0.31, 0.94	0.86	0.44, 1.67	1.12	0.59, 2.16	0.87	0.26, 2.93	0.92	0.54, 1.60
P for trend	<0.0001		0.08		0.63		0.36		0.32	
Waist circumference[c]										
Normal	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Increased	1.05	0.84, 1.30	1.11	0.82, 1.51	0.95	0.69, 1.31	0.96	0.55, 1.68	1.26	0.97, 1.63
Substantially increased	1.08	0.79, 1.48	1.52	1.01, 2.30	1.14	0.74, 1.75	1.04	0.48, 2.24	1.54	1.09, 2.19
P for trend	0.89		0.002		0.37		0.66		0.004	
WHR[d]										
Normal	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Moderate	1.07	0.88, 1.30	0.87	0.66, 1.14	0.82	0.61, 1.11	0.96	0.58, 1.58	1.11	0.88, 1.40
High	0.98	0.80, 1.20	1.13	0.87, 1.46	1.06	0.81, 1.40	1.19	0.71, 1.98	1.06	0.84, 1.34
P for trend	0.24		0.01		0.49		0.67		0.23	
Quartile of WHtR[e]										
1	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
2	0.95	0.72, 1.24	0.78	0.53, 1.16	1.16	0.74, 1.80	2.89	1.10, 7.58	1.15	0.81, 1.65
3	1.11	0.83, 1.49	0.92	0.61, 1.39	1.13	0.71, 1.81	3.21	1.17, 8.78	1.29	0.89, 1.87
4	1.16	0.79, 1.72	1.34	0.80, 2.24	1.25	0.70, 2.21	4.34	1.34, 14.1	1.52	0.96, 2.41
P for trend	0.30		0.007		0.24		0.22		0.02	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

[a] Calculated using Cox regression with age as the underlying time variable, stratification by center, age at recruitment, sex, and smoking status, and adjustment for the duration of smoking, the lifetime number of cigarettes smoked, the number of cigarettes smoked at baseline (all modeled with cubic spline functions), educational level, physical activity level, fruit consumption, vegetable consumption, meat consumption, fat intake, and energy intake. For waist circumference and WHtR, models were additionally adjusted for BMI.

[b] Weight (kg)/height $(m)^2$.

[c] The cutoffs for normal, increased, and substantially increased were <94.0, 94.0–101.9, and ≥102.0 cm, respectively, in men and <80 cm, 80 to <88 cm, and ≥88 cm, respectively, in women.

[d] The cutoffs for normal, moderate, and high were <0.950, 0.950–0.999, and >1.00, respectively, in men and <0.800, 0.800–0.849, and >0.850, respectively, in women.

[e] The cutoffs for quartiles 1–4 were <0.500, 0.500–0.539, 0.540–0.579, and ≥0.580, respectively, for men and <0.440, 0.440–0.479, 0.480–0.539, and ≥0.540, respectively, for women.

Former smokers had the highest average BMI, and current smokers had the lowest (Web Table 2). After conditioning on BMI, WC and WtHR were highest in current smokers and lowest in never smokers. This same pattern was seen for WHR in women.

BMI, hip circumference, and height were inversely related to lung cancer incidence in the crude model (Web Table 3), whereas WHR was positively related to lung cancer. The strength of the associations diminished after adjustment for smoking, with the association with lung cancer becoming nonsignificant for height and WHR (except in women). Taking other potentially confounding variables into account did not appreciably change the results (Web Table 3). After all adjustments, compared with normal-weight subjects, overweight subjects (BMI of 25.0–29.9) had a hazard ratio of 0.81 (95% confidence interval: 0.73, 0.90) and obese subjects (BMI of 30.0–34.9) had a hazard ratio of 0.72 (95% confidence interval: 0.62, 0.84) (Web Table 3). The *P* value for trend for BMI in the

Table 4. Hazard Ratio for the Associations of Lung Cancer With Body Mass Index, Waist Circumference, Waist-to-Hip Ratio, and Waist-to-Height Ratio by Years of Follow-Up, European Prospective Investigation Into Cancer and Nutrition, 1992–2010

Measure and Category	Years of Follow-Up							
	1–2 (*n* = 262)		3–5 (*n* = 515)		6–10 (*n* = 1,079)		11–17 (*n* = 544)	
	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI	HR[a]	95% CI
BMI[b]								
<18.5	2.10	0.80, 5.6	1.24	0.54, 2.85	1.51	0.79, 2.65	1.11	0.43, 2.85
18.5–24.9	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
25.0–29.9	0.85	0.62, 1.16	0.80	0.64, 1.00	0.75	0.65, 0.88	0.95	0.76, 1.20
30.0–34.9	0.70	0.43, 1.13	0.86	0.63, 1.16	0.68	0.57, 0.89	0.66	0.4, 0.98
≥35	0.35	0.11, 1.13	0.57	0.29, 1.12	0.94	0.68, 1.42	0.89	0.46, 1.71
P for trend		0.01		0.05		0.001		0.13
Waist circumference[c]								
Normal	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Increased	1.26	0.85, 1.87	1.10	0.83, 1.45	1.04	0.86, 1.25	1.06	0.80, 1.42
Substantially increased	1.91	1.12, 3.23	1.34	1.91, 1.96	1.18	0.94, 1.53	1.18	0.78, 1.78
P for trend		0.03		0.11		0.17		0.43
WHR[d]								
Normal	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Moderate	1.09	0.78, 1.52	1.17	0.92, 1.50	0.99	0.83, 1.17	0.80	0.61, 1.05
High	0.89	0.62, 1.27	1.13	0.88, 1.44	1.13	0.96, 1.34	0.89	0.68, 1.17
P for trend		0.62		0.22		0.14		0.32
Quartile of WHtR[e]								
1	1.00	Referent		1.00		Referent		1.00
2	1.55	0.89, 2.68	0.84	0.58, 1.23	1.03	0.81, 1.32	0.97	0.67, 1.40
3	2.01	1.12, 3.62	1.04	0.70, 1.53	1.02	0.78, 1.33	1.19	0.81, 1.76
4	2.91	1.41, 6.03	1.23	0.75, 2.00	1.27	0.92, 1.77	1.16	0.69, 1.95
P for trend		0.01		0.12		0.06		0.33

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

[a] Calculated using Cox regression with age as the underlying time variable, stratification by center, age at recruitment, sex, and smoking status, and adjustment for the duration of smoking, the lifetime number of cigarettes smoked, the number of cigarettes smoked at baseline (all modeled with cubic spline functions), educational level, physical activity level, fruit consumption, vegetable consumption, meat consumption, fat intake, energy intake, and height. For waist circumference and WHtR, models were additionally adjusted for BMI.

[b] Weight (kg)/height (m)^2.

[c] The cutoffs for normal, increased, and substantially increased were <94.0, 94.0–101.9, and ≥102.0 cm, respectively, in men and <80 cm, 80 to <88 cm, and ≥88 cm, respectively, in women.

[d] The cutoffs for normal, moderate, and high were <0.950, 0.950–0.999, and >1.00, respectively, in men and <0.800, 0.800–0.849, and >0.850, respectively, in women.

[e] The cutoffs for quartiles 1–4 were <0.500, 0.500–0.539, 0.540–0.579, and ≥0.580, respectively, for men and <0.440, 0.440–0.479, 0.480–0.539, and ≥0.540, respectively, for women.

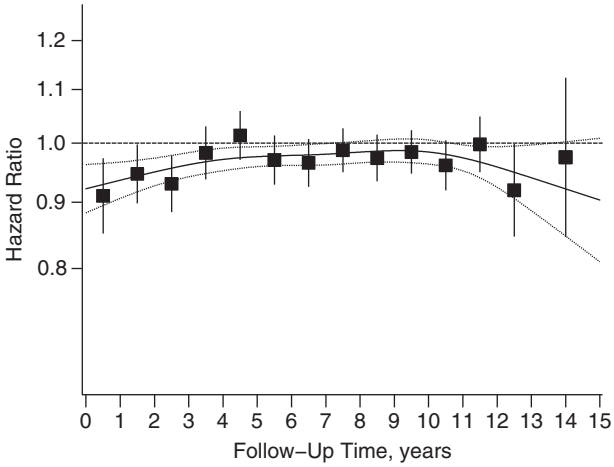

Figure 1. Fitted restricted cubic spline (with knots at 1, 4, 7, 10, and 13 years) for hazard ratios per 1-unit change in body mass index (measured as weight (kg)/height (m)^2; excluding underweight subjects) with time on follow-up, European Prospective Investigation of Cancer and Nutrition, 1992–2010. Results in this plot are adjusted for study center, age at recruitment, sex, smoking status (all as strata) and duration of smoking, the lifetime number of cigarettes smoked, and the number of cigarettes smoked at baseline (all modeled with cubic spline functions). Squares indicate hazard ratios for separate 1-year periods (last period: >13 year follow-up); dashed lines indicate 95% confidence intervals.

fully adjusted model remained significant after exclusion of those who were underweight (in men, $P = 0.0003$; in women, $P = 0.01$). These associations differed by smoking status (P for interaction trend test = 0.03) but were not modified by sex (P for interaction trend test = 0.47) or country (P for interaction trend test = 0.14).

After including BMI in the model, there was a positive, statistically significant association of WC and WHtR with lung cancer, but there was no association with hip circumference (Table 1). Compared with subjects with similar BMIs and normal waist circumferences, those with a substantially higher WC (≥94 cm for men, ≥88 cm for women) had a hazard ratio of 1.25 (95% confidence interval: 1.05, 1.50).

Statistically significant inverse associations of lung cancer with BMI and positive associations of lung cancer with WC and WHtR (after adjustment for BMI) were mainly seen in smokers (Table 2). However, the latter associations for WC and WHtR did not differ statistically significantly between the different smoking groups. For never smokers, the confidence intervals for the association between BMI and lung cancer completely contained the confidence intervals of the estimates for current smokers. In former smokers, there was no association with BMI and the hazard ratios differed significantly from those in smokers, whereas there was a positive association of lung cancer with WHR that was not seen in the other smoking groups.

Analysis by histological type revealed that the inverse association for BMI was strongest for adenocarcinoma ($P < 0.0001$) and was absent for small-cell carcinoma. The associations with the other histological types were of a strength similar to that seen for all lung cancers, but they were no longer statistically significant (Table 3). The trend tests for the positive relationships with abdominal fat indicators (WC and WHtR conditional on BMI and WHR) were all statistically significant for squamous-cell carcinoma, although for WHR, this was not reflected in the hazard ratios. The relationship between unclassified cases and WHtR (conditional on BMI) also reached statistical significance.

The number of adenocarcinomas in never smokers was large enough ($n = 114$) to justify analysis by smoking status. For adenocarcinomas, no interaction between any of the measures and smoking status was observed. For BMI, the inverse association with adenocarcinoma was significant in never smokers ($P = 0.01$) and current smokers ($P < 0.0001$) and borderline significant in former smokers ($P = 0.07$). The hazard ratios in never smokers were 1.12 (95% confidence interval: 0.15, 8.2) for subjects with a BMI <18.5, 0.81 (95% confidence interval: 0.54, 1.22) for subjects with a BMI of 25.0–29.9, 0.44 (95% confidence interval: 0.21, 0.89) for subjects with a BMI of 30.0–34.9, and 0.31 (95% confidence interval: 0.07, 1.32) for subjects with a BMI ≥35.0.

The inverse association between BMI and the risk of lung cancer was strongest in the first 3 years after baseline and declined in strength with increasing length of follow-up (Table 4; Figure 1). After exclusion of those who were underweight, the P values for trend for 0–2, 3–5, 6–10, or 11–17 years of follow-up were 0.02, 0.07, 0.003, and 0.12, respectively. For BMI and WC (after conditioning on BMI), the association was stronger in the first 3 years of follow-up than in the later period (for follow-up of <3 years, $P = 0.007$; for follow-up of ≥3 years, $P = 0.02$), whereas it was borderline statistically significant in the first 3 years for WtHR ($P = 0.05$). The hazard ratios, however, remained significant in the latter period, that is, when we excluded the first 3 years of follow-up. Over the entire time period, the interaction with time in follow-up as a continuous variable was not statistically significant: The lowest interaction P value was observed for BMI ($P = 0.2$).

We repeated all main analyses after excluding the anthropometric data based on self-report corrected with a predictive equation and case patients in whom the date of diagnosis was also date of death (results not shown), which yielded virtually the same results. When microscopically nonconfirmed cases were excluded, only slightly different results were found, most of which could be explained by the instability due to the lower number of cases.

DISCUSSION

In the present large-scale prospective cohort study, we observed an inverse association between lung cancer and BMI, whereas positive associations were found between indicators of abdominal fat (WHR (in women only) and WC and WHtR adjusted for BMI). The statistically significant associations were most consistently seen in current smokers, but for adenocarcinoma, a statistically significant association was also seen in never smokers. The associations diminished in strength after the first 3 years of follow-up.

The inverse association that we found between BMI and lung cancer risk is similar to findings in previous studies (1, 3–5, 8). A first explanation for the inverse association

between BMI and lung cancer risk that was observed even after detailed adjustment for smoking is that lung cancer could already be present at baseline in a preclinical stage, leading to weight loss before clinical diagnosis (6, 27, 30). This is corroborated by our finding that the strength of the association decreased after we excluded participants who were diagnosed in the first 3 years of follow-up. An inverse association even after 10–14 years of follow-up was previously reported in 3 studies (10, 16, 31), and stable risk estimates during a follow-up of 19 years were reported in another (32). Mathematical modeling suggests that tumor inception might occur approximately 13–14 years before people die from lung cancer (33), which suggests that preclinical disease is present many years before diagnosis. Another possible explanation for the weakening of the association is increasing misclassification, because some subjects' BMIs change after baseline. However, BMI ranking of subjects is relatively stable over time (34) and thus cannot explain the strong changes in risks seen in the first years of follow-up.

The question is whether the remaining long-term association is real or due to residual confounding by smoking or unobserved confounding. In the present study, adjustment for smoking habits was done using detailed information on current and past smoking and spline terms to make this adjustment as accurate as possible. Nevertheless, there might still be residual confounding of the analyses by smoking due to misclassification of exposure. Renehan et al. (7) calculated that a correlation of −0.1 between true BMI and true number of cigarettes smoked would be enough to explain the inverse association between BMI and lung cancer in the study of Smith et al. (8). In our data, the correlations of measured BMI with reported number of cigarettes smoked (lifetime or current) or duration of smoking were between −0.035 and −0.05. Because of measurement error, the correlations between the true entities will be higher. This implies that our results could also be considerably influenced by residual confounding.

Apart from misclassification of smoking at baseline, residual confounding could result from changes in smoking behavior after baseline. In a Danish study, Osler et al. (35) observed higher rates of smoking cessation among those with higher BMIs, which would lead to spuriously low hazard ratios in high BMI categories. However, it takes time for excess risk to decline after smoking cessation (36), so this can only influence the hazard ratios in the later years of follow-up. Although residual confounding by smoking thus will play a role in the observed inverse association between BMI and lung cancer, our finding that this association is strongest for adenocarcinomas suggests it might not fully explain the association because of all histological types, adenocarcinoma has the weakest association with smoking (37), and thus results for adenocarcinoma are less susceptible to residual confounding by smoking. In 2 recent case-control studies (38, 39), investigators also observed a stronger association of BMI with adenocarcinoma than with squamous-cell carcinoma, but in a cohort study (10), researchers observed the opposite. In a meta-analysis (which included that cohort study), Yang et al. (3) also observed a stronger association of BMI with squamous-cell carcinoma than with adenocarcinoma. Furthermore, there are also some biological explanations for an exclusive association in (former) smokers: Researchers have found more oxidative DNA damage as estimated by 8-hydroxydeoxyguanosine (40), by micronucleus frequency (2), or by aromatic DNA adducts (41) in leaner persons who smoke or are exposed to polycyclic aromatic hydrocarbons.

WHR in women, as well as WC and WHtR adjusted for BMI, were positively associated with the risk of lung cancer in our study. The finding that WC conditional on BMI is positively associated with lung cancer risk is consistent with findings from previous studies (6, 9, 10) and studies of cancer in general (42). The mechanism behind this finding for lung cancer is not clear. Having a higher WC than others with similar BMI and height is associated with more abdominal and specifically more visceral fat (43), in contrast to unadjusted WC, which correlates mostly with total fat (44). However, because keeping BMI and height constant implies keeping total mass constant, an increase in abdominal fat must be accompanied by a decrease in other parts of the body, like gluteofemoral fat or lean mass (45). A decrease in lean mass could well be associated with preclinical lung cancer, which could also explain our findings. Furthermore, WC and WtHR conditional on BMI and WHR in women were highest in smokers and lowest in never smokers (Web Table 2), which suggests that residual confounding by smoking might play a role. This is corroborated by our finding that higher abdominal fat indicators were most clearly associated with squamous-cell carcinoma and least associated with adenocarcinoma, consistent with a role of residual confounding by smoking, because small-cell and squamous-cell carcinomas are more strongly associated with lung cancer than are adenocarcinomas (37). In addition, Olson et al. (10) observed the strongest association between BMI and small-cell carcinoma, followed by BMI and squamous-cell carcinoma, whereas—like us—they did not observe a trend for adenocarcinoma.

The nonsignificant finding for WC and WHtR among never smokers could be due to lack of power, as the interaction with smoking was only statistically significant for WHR. In a previous study in never smokers, Lam et al. (9) observed a significant association between WC conditional on BMI and lung cancer incidence, suggesting that the association is not completely due to residual confounding by smoking.

Height was not associated with the risk of lung cancer in the present study. This is consistent with previous work, in which an association between height and lung cancer was found in only 2 out of 9 studies in which the association was assessed, and only in never smokers (6, 10, 15–21).

Strengths of our study are that we have detailed information on potential confounders and that anthropometric factors were mostly measured by trained professionals. To our knowledge, this is the first time the relationship between WHtR and lung cancer has been assessed. Important limitations are that the anthropometric factors and smoking were measured only at baseline and might have changed during follow-up.

In conclusion, we found that a higher BMI was inversely associated with the risk of lung cancer, whereas indicators of abdominal fat, that is, WHR (in women only) and WC and WHtR adjusted for BMI, were all positively associated with risk of lung cancer. Given that the strength of these associations declined with time in follow-up and that smoking measurements include some error, the associations will be at least partly due to weight loss caused by the presence of preclinical lung cancer at baseline and residual confounding by smoking.

ACKNOWLEDGMENTS

Authors affiliations: Department of Nutrition, Prevention and Health Care, National Institute for Public Health and the Environment, Bilthoven, the Netherlands (Nikmah Utami Dewi, Hendriek C. Boshuizen, H. Bas Bueno-de-Mesquita); Public Health Study Program, Tadulako University, Palu, Indonesia (Nikmah Utami Dewi); Department of Human Nutrition, Wageningen University, Wageningen the Netherlands (Hendriek C. Boshuizen, Ellen Kampman); Genetic Epidemiology Group, International Agency for Research on Cancer, Lyon, France (Mattias Johansson, Anouar Fanidi, David Muller); Department of Epidemiology and Biostatistics, the School of Public Health, Imperial College London, London, United Kingdom (Paolo Vineis, Petra H. Peeters, Amanda J. Cross, Teresa Norat, Elio Riboli, H. Bas Bueno-de-Mesquita); German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany (Annika Steffen, Heiner Boeing); Danish Cancer Society Research Center, Copenhagen, Denmark (Anne Tjønneland, Jytte Halkjær); Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark (Kim Overvad); Human Genetics Foundation, Torino, Italy (Gianluca Severi); INSERM, Centre for Research in Epidemiology and Population Health (CESP), Nutrition, Hormones and Women's Health Team, Villejuif, France (Guy Fagherazzi, Marie-Christine Boutron-Ruault); Université Paris Sud, Villejuif, France (Guy Fagherazzi, Marie-Christine Boutron-Ruault); Institut Gustave Roussy, Villejuif, France (Guy Fagherazzi, Marie-Christine Boutron-Ruault); Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany (Rudolf Kaaks, Kuanrong Li); Hellenic Health Foundation, Athens, Greece (Antonia Trichopoulou, Christina Bamia, Eleni Klinaki); Bureau of Epidemiologic Research, Academy of Athens, Athens, Greece (Antonia Trichopoulou); Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, Athens, Greece (Antonia Trichopoulou, Christina Bamia); Cancer Registry and Histopathology Unit, "Civic - M.P.Arezzo" Hospital, Azienda Sanitaria Provinciale di Ragusa, Italy (Rosario Tumino); Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute—ISPO, Florence, Italy (Domenico Palli); Dipartimento Di Medicina Clinica E Chirurgia Federico II University, Naples, Italy (Amalia Mattiello); Lombardy Cancer Registry Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy (Giovanna Tagliabue); Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands (Petra H. Peeters); Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands (Roel Vermeulen); Cancer Registry of Norway, Oslo, Norway (Elisabete Weiderpass); Department Community Medicine, UiT the Arctic University of Norway, Tromsø, Norway (Elisabete Weiderpass, Inger Torhild Gram); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (Elisabete Weiderpass); Department of Genetic Epidemiology, Folkhälsan Research Center, Helsinki, Finland (Elisabete Weiderpass); Department of Epidemiology, Murcia Regional Health Council, Murcia, Spain (José María Huerta); CIBER Epidemiología y Salud Pública, Spain (José María Huerta, María-José Sánchez, Eva Ardanaz); Unit of Nutrition, Environment and Cancer, Catalan Institute of Oncology-ICO, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain (Antonio Agudo); Escuela Andaluza de Salud Pública, Instituto de Investigación Biosanitaria de Granada, Hospitales Universitarios de Granada/Universidad de Granada, Granada, Spanish Public Health Directorate, Asturias, Spain (María-José Sánchez); Navarre Public Health Institute, Pamplona, Spain (Eva Ardanaz); Public Health Direction and Biodonostia Research Institute, Basque Regional Health Department, San Sebastian, Spain (Miren Dorronsoro); Public Health Directorate, Asturias, Spain (José Ramón Quirós); Department of Clinical Sciences, Diabetes and Cardiovascular Disease—Genetic Epidemiology CRC, University Hospital Malmö, Malmö, Sweden (Emily Sonestedt); Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom (Tim Key); Cambridge Institute of Public Health, School of Clinical Medicine, Radiation Sciences, Oncology, Umeå University, Umeå, Sweden (Mikael Johansson); Department of Medical Biosciences, Clinical Chemistry, Umeå University, Umeå, Sweden (Kjell Grankvist); Cancer Epidemiology Unit, University of Cambridge, Cambridge, United Kingdom (Kay-Tee Khaw); MRC Epidemiology Unit, University of Cambridge (Nick Wareham); Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, the Netherlands (H. Bas Bueno-de-Mesquita); and Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia (H. Bas Bueno-de-Mesquita).

The first 2 authors contributed equally to this paper.

The European Prospective Investigation Into Cancer and Nutrition was funded by "Europe Against Cancer" Programme of the European Commission; Ligue contre le Cancer (France); Institut Gustave Roussy (France); Mutuelle Générale de l'Education Nationale; Institut National de la Santé et de la Recherche Médicale (INSERM); German Cancer Aid; German Cancer Research Center; German Federal Ministry of Education and Research; Danish Cancer Society; Health Research Fund of the Spanish Ministry of Health; the participating regional governments and institutions of Spain; the Red Temática de Investigación Cooperativa en Cáncer of the Spanish Ministry of Health (Instituto de Salud Carlos III Red Tematica de Investigacion Cooperativa en Cancer grants R06/0020/0091 and RD12/0036/0018); Regional Government of Asturias; Cancer Research UK; Medical Research Council, United Kingdom; the Stroke Association, United Kingdom; British Heart Foundation; Department of Health, United Kingdom; Food Standards Agency, United Kingdom; the Wellcome Trust, United Kingdom; Hellenic Health Foundation; Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy Italian National Research Council; Dutch Ministry of Public Health, Welfare and Sports; Dutch Prevention Fund; LK Research Fund; Zorg Onderzoek Nederland; World Cancer Research Fund; Swedish Cancer Society; Swedish Scientific Council; Regional Government of Skane, Sweden; Norwegian Cancer Society; and County Council of Västerbotten, Sweden. D.M. was supported by an IARC Australia Fellowship from the International Agency for Research on Cancer and Cancer Council Australia.

Conflict of interest: none declared.

REFERENCES

1. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612): 569–578.
2. Li X, Bai Y, Wang S, et al. Association of body mass index with chromosome damage levels and lung cancer risk among males. *Sci Rep*. 2015;5:9458.
3. Yang Y, Dong J, Sun K, et al. Obesity and incidence of lung cancer: a meta-analysis. *Int J Cancer*. 2013;132(5):1162–1169.
4. Koh WP, Yuan JM, Wang R, et al. Body mass index and smoking-related lung cancer risk in the Singapore Chinese Health Study. *Br J Cancer*. 2010;102(3):610–614.
5. Bhaskaran K, Douglas I, Forbes H, et al. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. *Lancet*. 2014;384(9945):755–765.
6. Kabat GC, Kim M, Hunt JR, et al. Body mass index and waist circumference in relation to lung cancer risk in the Women's Health Initiative. *Am J Epidemiol*. 2008;168(2):158–169.
7. Renehan AG, Leitzmann MF, Zwahlen M. Re: "Body mass index and risk of lung cancer among never, former, and current smokers" [letter]. *J Natl Cancer Inst*. 2012;104(21): 1680–1681.
8. Smith L, Brinton LA, Spitz MR, et al. Body mass index and risk of lung cancer among never, former, and current smokers. *J Natl Cancer Inst*. 2012;104(10):778–789.
9. Lam TK, Moore SC, Brinton LA, 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.
10. Olson JE, Yang P, Schmitz K, et al. 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):606–615.
11. World Health Organization. *Waist Circumference and Waist–Hip Ratio: Report of a WHO Expert Consultation: Geneva, 8–11 December 2008*. Geneva, Switzerland: World Health Organization; 2011. http://apps.who.int/iris/bitstream/10665/44583/1/9789241501491_eng.pdf. Accessed June 15, 2016.
12. Molarius A, Seidell JC. Selection of anthropometric indicators for classification of abdominal fatness—a critical review. *Int J Obes Relat Metab Disord*. 1998;22(8):719–727.
13. Ashwell M, Hsieh SD. Six reasons why the waist-to-height ratio is a rapid and effective global indicator for health risks of obesity and how its use could simplify the international public health message on obesity. *Int J Food Sci Nutr*. 2005;56(5): 303–307.
14. Leitzmann MF, Moore SC, Koster A, et al. Waist circumference as compared with body-mass index in predicting mortality from specific causes. *PLoS One*. 2011;6(4):e18582.
15. Chyou P-H, Nomura AMY, Stemmermann GN. A prospective study of weight, body mass index and other anthropometric measurements in relation to site-specific cancers. *Int J Cancer*. 1994;57(3):313–317.
16. Tulinius H, Sigfússon N, Sigvaldason H, et al. Risk factors for malignant diseases: a cohort study on a population of 22,946 Icelanders. *Cancer Epidemiol Biomarkers Prev*. 1997;6(11): 863–873.
17. Hebert PR, Ajani U, Cook NR, et al. Adult height and incidence of cancer in male physicians (United States). *Cancer Causes Control*. 1997;8(4):591–597.
18. Cochrane AL, Moore F, Nomura A, et al. Body height and lung cancer risk. *Lancet*. 1983;321(8334):1162–1163.
19. Wynder EL, Goodman MT. Body height and lung cancer risk [letter]. *Lancet*. 1983;1(8334):1162.
20. Lee J, Kolonel LN. Body height and lung cancer risk [letter]. *Lancet*. 1983;1(8329):877.
21. Nomura A, Heilbrun LK, Stemmermann GN. Body height and lung cancer risk [letter]. *Lancet*. 1983;8329(877):1162.
22. Riboli E, Kaaks R. The EPIC Project: rationale and study design. European Prospective Investigation Into Cancer and Nutrition. *Int J Epidemiol*. 1997;26(suppl 1):S6–S14.
23. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation Into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr*. 2002; 5(6B):1113–1124.
24. Haftenberger M, Lahmann PH, Panico S, et al. Overweight, obesity and fat distribution in 50- to 64-year-old participants in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *Public Health Nutr*. 2002;5(6B):1147–1162.
25. Thiébaut ACM, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med*. 2004;23(24):3803–3820.
26. Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. *Comput Methods Programs Biomed*. 1997;54(3):201–208.
27. World Cancer Research Fund/American Institute of Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. Washington, DC: AICR; 2007. http://www.aicr.org/assets/docs/pdf/reports/Second_Expert_Report.pdf. Accessed June 15, 2016.
28. Menvielle G, Boshuizen H, Kunst AE, et al. The role of smoking and diet in explaining educational inequalities in lung cancer incidence. *J Natl Cancer Inst*. 2009;101(5): 321–330.
29. Wareham NJ, Jakes RW, Rennie KL, et al. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation Into Cancer and Nutrition (EPIC) study. *Public Health Nutr*. 2003;6(4):407–413.
30. Henley SJ, Flanders WD, Manatunga A, et al. Leanness and lung cancer risk: fact or artifact? *Epidemiology*. 2002;13(3):268–276.
31. Knekt P, Heliövaara M, Rissanen A, et al. Leanness and lung-cancer risk. *Int J Cancer*. 1991;49(2):208–213.
32. Samanic C, Chow WH, Gridley G, et al. Relation of body mass index to cancer risk in 362,552 Swedish men. *Cancer Causes Control*. 2006;17(7):901–909.
33. van Dillen T, Dekkers F, Bijwaard H, et al. Lung cancer from radon: a two-stage model analysis of the WISMUT Cohort, 1955–1998. *Radiat Res*. 2011;175(1):119–130.
34. Bayer O, Krüger H, von Kries R, et al. Factors associated with tracking of BMI: a meta-regression analysis on BMI tracking. *Obesity (Silver Spring)*. 2011;19(5):1069–1076.
35. Osler M, Prescott E, Godtfredsen N, et al. Gender and determinants of smoking cessation: a longitudinal study. *Prev Med*. 1999;29(1):57–62.
36. Fry JS, Lee PN, Forey BA, et al. How rapidly does the excess risk of lung cancer decline following quitting smoking? A quantitative review using the negative exponential model. *Regul Toxicol Pharmacol*. 2013;67(1):13–26.
37. Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. *Lung Cancer*. 2001; 31(2-3):139–148.
38. El-Zein M, Parent ME, Nicolau B, et al. Body mass index, lifetime smoking intensity and lung cancer risk. *Int J Cancer*. 2013;133(7):1721–1731.
39. Tarnaud C, Guida F, Papadopoulos A, et al. Body mass index and lung cancer risk: results from the ICARE study, a large, population-based case-control study. *Cancer Causes Control*. 2012;23(7):1113–1126.

40. Mizoue T, Kasai H, Kubo T, et al. Leanness, smoking, and enhanced oxidative DNA damage. *Cancer Epidemiol Biomarkers Prev*. 2006;15(3):582–585.
41. Godschalk RW, Feldker DE, Borm PJ, et al. Body mass index modulates aromatic DNA adduct levels and their persistence in smokers. *Cancer Epidemiol Biomarkers Prev*. 2002;11(8): 790–793.
42. Oppert JM, Charles MA, Thibult N, et al. Anthropometric estimates of muscle and fat mass in relation to cardiac and cancer mortality in men: the Paris Prospective Study. *Am J Clin Nutr*. 2002;75(6):1107–1113.
43. Janssen I, Heymsfield SB, Allison DB, et al. Body mass index and waist circumference independently contribute to the prediction of nonabdominal, abdominal subcutaneous, and visceral fat. *Am J Clin Nutr*. 2002;75(4):683–688.
44. Neamat-Allah J, Wald D, Hüsing A, et al. Validation of anthropometric indices of adiposity against whole-body magnetic resonance imaging—a study within the German European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts. *PLoS One*. 2014;9(3):e91586.
45. Moore SC. Waist versus weight—which matters more for mortality? *Am J Clin Nutr*. 2009;89(4):1003–1004.