

Body mass index and the risk of cancer incidence in patients with type 2 diabetes in Japan: Results from the National Center Diabetes Database

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ABSTRACT

Aims/Introduction: Both type 2 diabetes and obesity increase the risk of some types of cancers, and underlying mechanisms are thought to be, at least in part, common. In the present study, we carried out a retrospective cohort study of the relationship between body mass index (BMI) categories and cancer development in Japanese type 2 diabetic patients.

Materials and Methods: A total of 113 incident cancers including 35 cancers whose incidence was reported to be increased by obesity (27 colorectal cancers, two breast cancers in postmenopausal women, one endometrial cancer, four renal cancers and one gallbladder cancer) were identified in 2,334 type 2 diabetic patients (1,616 men and 718 women) over an average observation period of 5.1 years.

Results: In men, there was no significant association between the BMI categories at the start of the observation period and the development of any cancer. In contrast, the incidence of all of the cancers in the women was significantly higher in the group with a BMI of less than 22.0 kg/m² (hazard ratio 3.07, 95% CI 1.01–9.36). In either sex, there was no significant relationship between the BMI categories and the development of cancers whose risk is known to be increased by obesity.

Conclusions: The findings of the present study were limited by the relatively small number of patients in the cohort, which posed a danger of not finding significance. However, the results suggested that obesity did not become an additional risk factor for cancer in Japanese type 2 diabetic patients.

INTRODUCTION

Both type 2 diabetes and obesity have been considered to be associated with an increased risk of certain types of cancer, and the underlying mechanisms, such as hyperinsulinemia as a result of insulin resistance, are thought to be shared, at least in part^{1–4}. Therefore, type 2 diabetes and obesity are likely to additively influence cancer development.

Obese individuals have higher degrees of insulin resistance than lean individuals, both in the type 2 diabetic population and the general population^{5,6}. Plasma levels of inflammatory markers and adipocytokines, which have been shown to be related to the development of breast cancer, are reported to be correlated with body mass index (BMI) in women, both those with and without type 2 diabetes⁷. However, only a few clinical reports have examined the combined effect of type 2 diabetes and obesity on the risk of cancer^{8–10}, and not all reports have been able to verify that cancer risk is higher in obese diabetic patients.

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In the present study, we carried out a retrospective cohort study of the risk of cancer development by BMI category, using BMI as a surrogate marker of obesity, in type 2 diabetic patients registered in the National Center Diabetes Database. BMI is known to be correlated with the plasma levels of adipocytokines^{7,11,12} and mediators of inflammation¹³, whose production is increased in cases of obesity. Accordingly, BMI is frequently used as a surrogate marker of leanness/obesity in epidemiological studies.

MATERIALS AND METHODS

Population included in the analysis

The structure of the National Center Diabetes Database has been described in detail previously¹⁴. To examine the conditions related to malignant neoplasms occurring in type 2 diabetes patients registered in this database, we set up a retrospective cohort. We first extracted data for 3,807 type 2 diabetes patients who had received treatment in 2008 and 2009

(start of observation) at three institutions (Center Hospital, National Center of Global Health and Medicine; Konodai Hospital, National Center of Global Health and Medicine; and the Institute of Adult Disease, Asahi Life Foundation) where information on the presence, absence or new onset of cancer in all patients is registered. Next, of the 3,807 patients, 731 for whom information on the smoking status, drinking habit, height and weight, or values of hemoglobin A1c was missing were excluded. To avoid the influence of cancer growth on the clinical and biochemical parameters, we also excluded data for 527 patients who had been diagnosed as having cancer before or within 12 months of the start of the observation. We also excluded 215 patients who discontinued their outpatient clinic visits within 12 months of the start of the observation. After these exclusions, the data of 2,334 patients with recorded information on the presence, absence or new onset of cancer, the smoking status, drinking habit, height and weight, and values of hemoglobin A1c were finally selected for this study (Fig. 1).

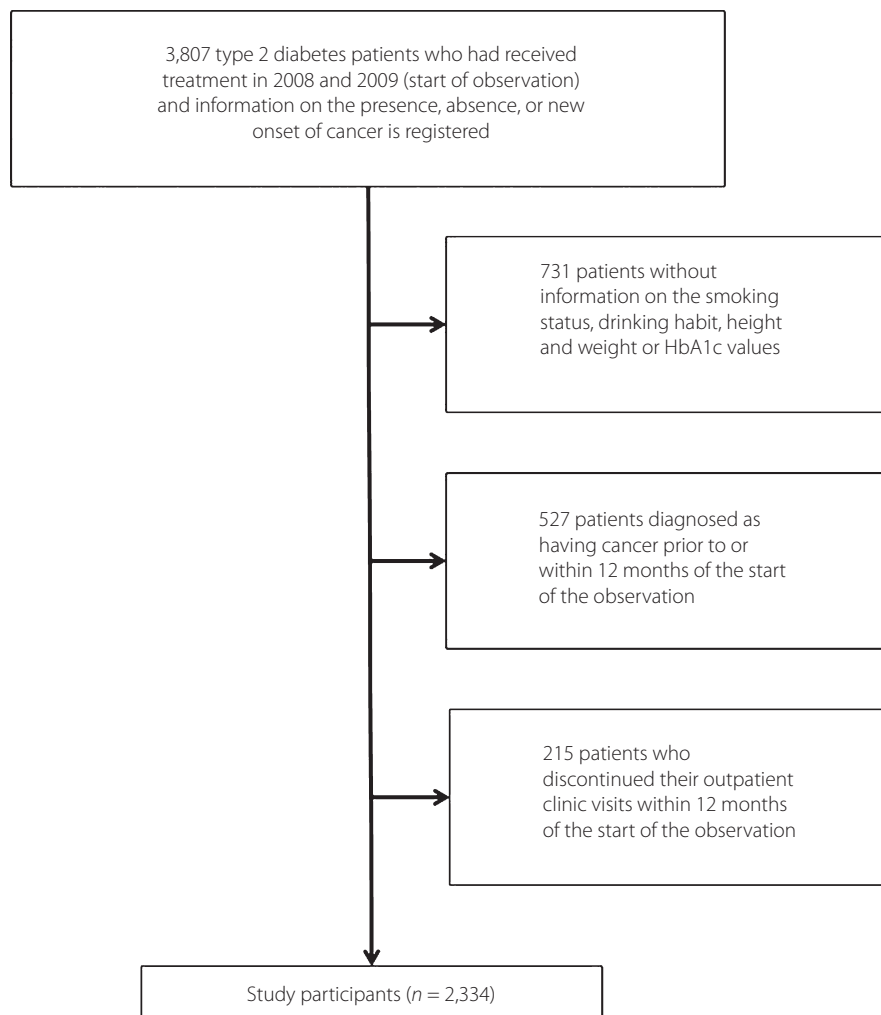


Figure 1 | Flowchart for the selection of the study population included in the analysis. HbA1c, hemoglobin A1c.

Study variables

The cohort of 2,334 patients was observed from the start of the observation period until the new onset of malignant tumors (end-point of this study), dropout or the end of 2013. The new onset of malignant tumors was identified from the registered data. The data were then analyzed to determine: (i) the risk of all cancers; and (ii) the risk of cancers for which the incidence was reportedly increased by obesity (cancers of the colorectum, breast in postmenopausal women, endometrium, kidney, thyroid and gall bladder, as well as esophageal adenocarcinoma)¹⁵. If data at the start of the observation period had not been obtained, data from a time closest to the start of the observation period were used.

This research conformed to 'Ethical Guidelines for Medical and Health Research involving Human Subjects' issued by the Ministry of Health, Labor and Welfare of Japan, and was approved by the National Center for Global Health and Medicine Research Ethics Committee.

Statistical analysis

The data analysis was carried out using R version 3.2.1 (Statistical Computing, Vienna, Austria)¹⁶. Continuous variables were summarized as the mean \pm standard deviation (for variables showing normal distribution) or the median and the 25–75th percentiles (for variables not showing a normal distribution). Weight (in kilograms) was divided by the square of height (in meters) to calculate the BMI, and the values were rounded to three significant digits. The Japan Society for the Study of Obesity defines a BMI of 22.0 kg/m² as the ideal bodyweight based on previous studies revealing that people with a BMI of 22.0 kg/m² showed the highest degree of freedom from disease and the lowest morbidity¹⁷. Accordingly, the Japan Diabetes Society also uses this ideal bodyweight as a treatment goal¹⁸, and in Japanese people, a BMI of 25.0 kg/m² or greater is defined as obesity¹⁹; therefore, the patients in the present cohort were divided into three groups for analysis: a group with a BMI of less than the ideal bodyweight (less than 22.0 kg/m²), a group with a BMI of 22.0 to less than 25.0 kg/m², and a group with obesity (25.0 kg/m² or greater).

A multivariate Cox regression analysis was carried out to estimate the hazard ratios (HR) with the corresponding 95% confidence intervals (95% CI) for cancer incidence associated with BMI category. Calculations were carried out using the group with a BMI of 22.0 to less than 25.0 kg/m² as the reference group. The model was adjusted for age, smoking status and drinking habits. Participants were divided according to their smoking status into never smokers, current smokers and former smokers. Considering the report by Inoue and Tsugane²⁰ that heavy drinking is associated with cancer risk in Japanese people, the participants were also divided into two categories according to their drinking habit: a group of participants who drank on less than 3 days of the week and a group of participants who drank on 3 days or more of the week. Associations were also adjusted for age used as the continuous

variable. *P*-values less than 0.05 were considered statistically significant.

RESULTS

Of 2,334 patients, 1,616 were men and 718 were women, with a median age at study entry of 62.0 years for men and 66.0 years for women. The average time of follow up was 5.1 years, with a total of 11 835.1 person-years. The demographics of patients by BMI category are presented in Table 1. By the end of 2013, a total of 113 incident cancers had been diagnosed (Table 2). Hemoglobin A1c levels at the start of the observation period were not associated with the risk of cancer (adjusted for age, smoking status and drinking habit; men: hazard ratio 1.01, 95% CI 0.86–1.17; women: hazard ratio 1.00, 95% CI 0.74–1.36).

Calculations using the group with a BMI of 22.0 to less than 25.0 kg/m² as the reference group showed that there was no significant association between the BMI categories and the development of any type of cancer in men (Table 3). In women, a Cox regression analysis adjusted for age, smoking, and frequency of alcohol consumption showed that cancer risk was higher in women with a BMI of less than 22.0 kg/m² than in those with a BMI of 22.0 to less than 25.0 kg/m² (hazard ratio 3.07, 95% CI 1.01–9.36; Table 3). In the present cohort, the risk of cancers whose risk of development is known to be increased by obesity was not higher in the group with a BMI of 25.0 kg/m² or greater (Table 3).

DISCUSSION

Diabetic patients have an elevated cancer risk^{1,21,22}, whereas obesity is also known to increase the risk of some types of cancer in the general population^{15,23–25}. In the present study, we stratified type 2 diabetic patients by BMI to investigate the risk of all cancers and also the risk of those cancers whose incidence is known to be increased by obesity. However, the risk of these cancers was not found to be increased in the group with a BMI of 25.0 kg/m² or greater in this study.

There have been a limited number of reports examining the combined effect of type 2 diabetes and BMI on the risk of cancer incidence or mortality, and conflicting results have been reported from these studies. Jee *et al.*⁸ reported an association between the fasting serum glucose level and the risk of death from liver cancer, and suggested that this association was not modified by obesity. Moe and Lund-Nilsen⁹ investigated the risk of development of cancer in diabetic patients, and showed that the cancer risk was higher in the group with low physical activity and the group with a BMI of 25.0 kg/m² or greater. Seow *et al.*¹⁰ reported that the risk of colorectal cancer was higher in diabetic patients with a BMI of 20 to less than 24 kg/m², but not elevated in diabetic patients with a BMI of greater than 24 kg/m².

Insulin resistance, observed in both obese individuals and type 2 diabetic patients, is known to be related to cancer cell growth². Why is an additive effect not observed when these

Table 1 | Demographics of patients stratified according to body mass index

	Men			Women		
	Body mass index			Body mass index		
	<22.0	≥22.0 to <25.0	≥25.0	<22.0	≥22.0 to <25.0	≥25.0
No. patients	478	539	599	228	197	293
Median age at entry, years (interquartile range)	65.2 (59.4–72.0)	63.4 (57.0–69.7)	58.7 (50.1–66.5)	70.0 (62.6–75.8)	66.7 (61.0–73.7)	63.8 (56.3–71.1)
Mean follow-up period (years)	5.0 ± 1.4	5.1 ± 1.3	5.1 ± 1.4	4.9 ± 1.5	5.2 ± 1.2	5.2 ± 1.3
Smoking status (%)						
Never	22.0	22.1	25.9	75.5	75.1	60.4
Former	35.5	35.0	34.1	8.8	10.7	17.4
Current	42.5	42.9	40.0	15.7	14.2	21.8
Drinking habits (%)						
>3 days/week	53.8	53.8	59.3	89.1	91.4	89.4
≤3 days/week	46.2	46.2	40.7	10.9	8.6	10.6
Median HbA1c, % (interquartile range)	7.4 (6.7–8.2)	7.5 (6.9–8.4)	7.6 (6.8–8.7)	7.3 (6.7–8.0)	7.3 (6.8–8.0)	7.45 (6.8–8.3)
Median non-high-density lipoprotein cholesterol, mg/dL (interquartile range, n = 1,909)	128 (109–149)	139 (120–162)	141 (122–166)	138 (117–155.5)	145 (121.5–166)	147.5 (128–166)
No. cancers	29	37	22	14	4	7

HbA1c, hemoglobin A1c.

two factors present concomitantly in a clinical setting? Other habitual factors, such as the level of intake of vegetable and fruit^{26,27}, exercise habit²⁸ or factors associated with diabetes, such as antidiabetic drugs, might have a stronger influence than BMI in determining the risk of cancer. Future studies are required to assess the possible modification of the cancer risk by these factors.

In the present study, analysis of type 2 diabetic women showed that the cancer risk was higher in the group with a BMI of less than 22.0 kg/m² than in the reference category. Types of cancer associated with leanness are known in people in general, although no such association has been reported in type 2 diabetic patients. The risk of development of cancer of the head and neck is reported to be negatively correlated with BMI²⁹. Renehan *et al.*³⁰ reported through a meta-analysis that the risks of development of lung cancer, esophageal squamous cell carcinoma and premenopausal breast cancer are also negatively correlated with BMI. The FINRISK study reported a negative correlation between BMI and the risk of development of lung cancer and breast cancer in women, and the existence of a J-curve relationship between BMI and the risk of all cancers in women³¹. The influence of BMI on the development of some types of cancer appears to be affected by sex differences and sex hormones.^{32,33} Hou *et al.*³² reported that the risk of colon cancer is correlated with BMI in men and premenopausal women, and negatively correlated with BMI in postmenopausal women. In the future, it would be desirable to analyze the data of a larger number of patients to clarify whether the aforementioned findings in the general population are also applicable to type 2 diabetic patients.

We admit that the present study had several limitations. First, we do not have data regarding waist circumferences, body fat content, values of inflammatory mediators, adipocytokines or indices of insulin resistance for the participants. Second, the results of this study were limited by the relatively small number of patients in the cohort, which poses a danger of not finding significance. Finally, the 5-year observation period with this sample size was too short to obtain enough events of occurrence. Therefore, it is necessary in the future to analyze the data of a larger number of patients by pooled analyses of similar studies.

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Table 2 | Incident cancers during the observation period

	Men			Women		
	Body mass index			Body mass index		
	<22.0	≥22.0 to <25.0	≥25.0	<22.0	≥22.0 to <25.0	≥25.0
Oropharynx	2	0	1	1	0	0
Submandibular gland	0	0	1	0	0	0
Larynx	1	1	0	0	0	0
Esophageal (squamous cell cancer)	2	1	0	0	0	0
Stomach	3	7	3	2	0	1
Duodenum	0	1	0	0	0	0
Colorectal [†]	6	7	7	3	1	3
Liver	2	0	1	0	0	0
Gall bladder [†]	1	0	0	0	0	0
Biliary tract	0	0	0	2	0	0
Pancreas	1	4	0	1	0	1
Lung	2	4	4	2	0	1
Breast (postmenopausal) [†]	0	0	0	2	0	0
Endometrial [†]	0	0	0	0	0	1
Ovary	0	0	0	1	1	0
Prostate	5	5	2	0	0	0
Kidney [†]	2	2	0	0	0	0
Renal pelvis	0	1	0	0	0	0
Urinary bladder	1	2	1	0	1	0
Hematopoietic	0	2	2	0	0	0
Gastric gastrointestinal stromal tumor	0	0	0	0	1	0
Adenocarcinoma of unknown origin	1	0	0	0	0	0

The table shows the types of cancer by the sex and body mass index category in the 113 cases of cancer diagnosed by the end of 2013. [†]Cancers whose incidences are known to be increased by obesity in the general population¹⁵.

Table 3 | Cox proportional hazards regression analysis with body mass index adjusted for age, smoking and frequency of alcohol consumption

	Body mass index		
	<22.0	≥22.0 to <25.0 (reference)	≥25.0
Total cancers			
Men			
HR (95% CI)	0.82 (0.50–1.33) <i>P</i> = 0.41	1	0.67 (0.39–1.13) <i>P</i> = 0.13
Women			
HR (95% CI)	3.07 (1.01–9.36) <i>P</i> = 0.048	1	1.38 (0.40–4.78) <i>P</i> = 0.61
Cancers for which the incidence is increased by obesity			
Men			
HR (95% CI)	1.05 (0.42–2.67) <i>P</i> = 0.91	1	0.84 (0.31–2.29) <i>P</i> = 0.74
Women			
HR (95% CI)	6.11 (0.75–49.8) <i>P</i> = 0.09	1	3.11 (0.34–28.1) <i>P</i> = 0.31

An analysis was carried out to estimate the hazard ratios (HR) with the corresponding 95% confidence intervals (95% CI) for cancer incidence associated with body mass index. Reference categories were participants with a body mass index between 22.0 and 25 kg/m². The model was adjusted for age, smoking status and drinking habits. Cancers whose risk are known to be increased by obesity in the general population are cancers of the colorectum, breast in postmenopausal women, endometrium, kidney, thyroid and gall bladder, and esophageal adenocarcinoma¹⁵.

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DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Kasuga M, Ueki K, Tajima N, *et al.* Report of the JDS/JCA joint committee on Diabetes and Cancer. *Diabetol Int* 2013; 4: 81–96.
2. Gallagher EJ, LeRoith D. Obesity and diabetes: the increased risk of cancer and cancer-related mortality. *Physiol Rev* 2015; 95: 727–748.
3. Otani T, Iwasaki M, Sasazuki S, *et al.* Plasma C-peptide, insulin-like growth factor-I, insulin-like growth factor binding proteins and risk of colorectal cancer in a nested case-control study: the Japan public health center-based prospective study. *Int J Cancer* 2007; 120: 2007–2012.
4. Nead KT, Sharp SJ, Thompson DJ, *et al.* Evidence of a causal association between Insulinemia and Endometrial Cancer: a mendelian randomization analysis. *J Natl Cancer Inst* 2015; 107: djv178.
5. Matsumoto K, Miyake S, Yano M, *et al.* Glucose tolerance, insulin secretion, and insulin sensitivity in nonobese and obese Japanese subjects. *Diabetes Care* 1997; 20: 1562–1568.
6. Yamamoto-Honda R, Osame K, Kitazato H, *et al.* Insulin secretion and insulin sensitivity in Japanese patients with type 2 diabetes: a cross-sectional study comparing the homeostasis model assessment-2 (HOMA2) indexes and indexes derived from the oral glucose tolerance test. *Diabetology Int* 2011; 2: 72–78.
7. Alokail MS, Al-Daghri NM, Al-Attas OS, *et al.* Combined effects of obesity and type 2 diabetes contribute to increased breast cancer risk in premenopausal women. *Cardiovasc Diabetol* 2009; 8: 33.
8. Jee SH, Ohrr H, Sull JW, *et al.* Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005; 293: 194–202.
9. Moe B, Lund-Nilsen TI. Cancer risk in people with diabetes: does physical activity and adiposity modify the association? Prospective data from the HUNT Study, Norway. *J Diabetes Complications* 2015; 29: 176–179.
10. Seow A, Yuan J-M, Koh W-P, *et al.* Diabetes mellitus and risk of colorectal cancer in the Singapore Chinese Health Study. *J Natl Cancer Inst* 2006; 98: 135–138.
11. Cnop M, Havel PJ, Utzshneider KM, *et al.* Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia* 2003; 46: 459–469.
12. Kennedy A, Gettys TW, Watson P, *et al.* The metabolic significance of leptin in humans: gender-based differences in relationships to adiposity, insulin sensitivity, and energy expenditure. *J Clin Endocrinol Metab* 1997; 82: 1293–1300.
13. Kitahara CM, Trabert B, Katki HA, *et al.* Body mass index, physical activity, and serum markers of inflammation, immunity, and insulin resistance. *Cancer Epidemiol Biomarkers Prev* 2014; 23: 2840–2849.
14. Yamamoto-Honda R, Takahashi Y, Yamashita S, *et al.* Constructing the National Center Diabetes Database. *Diabetol Int* 2014; 5: 234–243.
15. National Cancer Institute. Obesity and Cancer Risk. Available from: <http://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet> Accessed April 22, 2016.
16. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2015. Available from: <http://www.R-project.org/> Accessed April 22, 2016.
17. Tokunaga K, Matsuzawa Y, Kotani K, *et al.* Ideal body weight estimated from the body mass index with the lowest morbidity. *Int J Obes* 1991; 15: 1–5.
18. Japan Diabetes Society. Treatment objectives and control indicators. In: Japan Diabetes Society (ed). *Treatment Guide for Diabetes 2012–2013*. Tokyo: Bunko-do, 2012; 13–15.
19. Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J* 2002; 66: 987–992.
20. Inoue M, Tsugane S; JPHC Study Group. Impact of alcohol drinking on total cancer risk: data from a large-scale population-based cohort study in Japan. *Br J Cancer* 2005; 92: 182–187.
21. Sasazuki S, Charvat H, Hara A, *et al.* Diabetes mellitus and cancer risk: pooled analysis of eight cohort studies in Japan. *Cancer Sci* 2013; 104: 1499–1507.
22. Tanaka K, Tsuji I, Tamakoshi A, *et al.* Diabetes mellitus and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Jpn J Clin Oncol* 2014; 44: 986–999.
23. Sasazuki S, Inoue M, Tsuji I, *et al.* Results of a pooled analysis of 7 large-scale cohort studies. *J Epidemiol* 2011; 21: 417–430.
24. Matsuo K, Mizoue T, Tanaka K, *et al.* Development and evaluation of cancer prevention strategies in Japan. *Ann Oncol* 2012; 23: 479–490.
25. Wada K, Nagata C, Tamakoshi A, *et al.* Body mass index and breast cancer risk in Japan: a pooled analysis of eight population-based cohort studies. *Ann Oncol* 2014; 25: 519–524.
26. Wakai K, Sugawara Y, Tsuji I, *et al.* Risk of lung cancer and consumption of vegetables and fruit in Japanese: a pooled analysis of cohort studies in Japan. *Cancer Sci* 2015; 106: 1057–1065.
27. Shimazu T, Wakai K, Tamakoshi A, *et al.* Association of vegetable and fruit intake with gastric cancer risk among Japanese: a pooled analysis of four cohort studies. *Ann Oncol* 2014; 25: 1228–1233.

28. Sawada SS, Lee IM, Naito H, *et al.* Cardiorespiratory fitness, body mass index, and cancer mortality: a cohort study of Japanese men. *BMC Public Health* 2014; 14: 1012.
29. Maasland DH, van den Brandt PA, Kremer B, *et al.* Body mass index and risk of subtypes of head-neck cancer: the Netherlands Cohort Study. *Sci Rep* 2015; 5: 17744.
30. Renahan 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: 569–578.
31. Song X, Pukkala E, Dyba T, *et al.* Body mass index and cancer incidence: the FINRISK study. *Eur J Epidemiol* 2014; 29: 477–487.
32. Hou L, Ji BT, Blair A, *et al.* Body mass index and colon cancer risk in Chinese people: menopause as an effect modifier. *Eur J Cancer* 2006; 42: 84–90.
33. Pesatori AC, Carugno M, Consonni D, *et al.* Hormone use and risk for lung cancer: a pooled analysis from the International Lung Cancer Consortium (ILCCO). *Br J Cancer* 2013; 109: 1954–1964.