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Metabolic Syndrome and Total Cancer Mortality in the Third National Health and Nutrition Examination Survey

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Abstract

Purpose—Although metabolic syndrome incidence has substantially increased during the last few decades, it largely remains unclear whether this metabolic disorder is associated with total cancer mortality. The present study was carried out to investigate this important question.

Methods—A total of 687 cancer deaths were identified from 14,916 participants in the third National Health and Nutrition Examination Survey by linking them to the National Death Index database through December 31, 2006. Cox proportional hazards regression was performed to calculate hazard ratios (HR) and 95% confidence intervals (CI) for total cancer mortality in relation to metabolic syndrome and its individual components.

Results—After adjustment for confounders, a diagnosis of metabolic syndrome was associated with 33% elevated total cancer mortality. Compared with individuals without metabolic syndrome, those with 3, 4 and 5 abnormal components had HRs (95% CIs) of 1.28 (1.03–1.59), 1.24 (0.96–1.60), and 1.87 (1.34–2.63), respectively (p-trend = 0.0003). Systolic blood pressure and serum glucose were associated with an increased risk of death from total cancer [HR (95% CI) for highest vs. lowest quartiles: 1.67 (1.19–2.33), p-trend = 0.002 and 1.34 (1.04–1.74), p-trend = 0.003, respectively]. Overall null results were obtained for lung cancer mortality. The effects of metabolic syndrome and its components on non-lung cancer mortality were generally similar to, but somewhat larger than, those for total cancer mortality.

Conclusion—Our study is among the first to reveal that metabolic syndrome is associated with increased total cancer mortality.

Keywords

metabolic syndrome; obesity; total cancer mortality; lung cancer mortality; non-lung cancer mortality; cohort study; epidemiology

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Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Introduction

Cancer is a leading cause of death in both developed and developing countries. It was reported that 14.1 million cancer cases and 8.2 million cancer deaths occurred worldwide in 2012 [1]. On a global scale, cancers of the breast and the lung are most common in women and men, respectively [1]. The American Cancer Society has estimated that there were 1,658,370 new cancer cases and 589,430 cancer deaths in the U.S. in 2015 [2]. Prostate cancer is the most commonly diagnosed cancer among American men, while lung cancer remains the leading cause of cancer death in both sexes [2]. Given the tremendous medical and economic burden of cancer on the world population, it is critically urgent to identify modifiable risk factors for its prevention and control.

Obesity is increasing at epidemic proportions in developed countries and at an alarming pace in developing countries [1]. It is reported that more than one billion adults are overweight and 315 million are obese worldwide [3]. In the U.S., more than one third (36%) of adults are obese [3]. Obesity is the major determinant of metabolic syndrome, an abnormal health condition that is well established as a precursor to type 2 diabetes mellitus and linked to the risk of several cancers [4–6]. Metabolic syndrome is defined as a cluster of at least three of the following five factors: high-density lipoprotein (HDL) cholesterol (<40 mg/dl for men and <50 mg/dl for women), triglycerides (>150 mg/dl), systolic blood pressure (>130 mm Hg), blood glucose (>100 mg/dl), and waist circumference (>102 cm for men and >88 cm for women) [7]. Metabolic syndrome is common in Western populations, with a prevalence of approximately 25% in the U.S. [8, 9].

A number of epidemiologic studies have showed that obesity is associated with an increased risk of colorectal, kidney, gallbladder, endometrial, prostate, and post-menopausal breast cancer [10, 11]. Some studies also revealed that obesity increased all-cause and total cancer mortality [12–16]. However, epidemiological data on the association between metabolic syndrome and cancer have been relatively scarce and inconsistent. In some studies, metabolic syndrome was found to modulate total cancer mortality in men [17, 18] but not in women [18]. Some other studies have evaluated the influence of individual metabolic syndrome components on cancer mortality, with mixed results [19–22]. Although investigating metabolic syndrome and its individual components in relation to cancer risk may shed light on the biological mechanisms by which obesity alters carcinogenesis [17], no epidemiologic studies have systematically examined this research question in a national representative sample of the general U.S. population. Therefore, the present study sought to evaluate whether metabolic syndrome and its individual components are associated with total cancer mortality in the Third National Health and Nutrition Examination Survey (NHANES III).

Materials and Methods

Study subjects

Data collected from the NHANES III (1988–1994) were analyzed in the present study. NHANES III was conducted by the U.S. National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). The survey design and methodology of

the NHANES III have been described in detail elsewhere [23]. Death from cancer for each of the participants was ascertained by a probabilistic match between NHANES III database and the death certificate records of the U.S. National Death Index [23]. The follow-up period for each subject was calculated as the time from the date of health examination to the occurrence of cancer death or the censor date (December 31, 2006), whichever occurred first. Total cancer mortality included deaths from all sites of cancer defined by the 9th revision of the International Classification of Diseases (ICD).

Data on the individual components of metabolic syndrome were available from 19,618 participants aged 18 years or older. A total of 322 pregnant women were excluded because of increased waist circumference and potential metabolic changes following pregnancy. Given the objective of the present study, participants who died from a cancer diagnosed at baseline (i.e. date of health examination) (n=190) also were excluded from analysis. These exclusions led to 19,106 participants in the cohort. A total of 946 cases of cancer deaths were documented from the 19,106 participants during a follow-up of 250,443 person-years. The anatomic sites of cancer for the 946 cases included cancers of the lung (n = 279), colon and rectum (n = 93), prostate (n = 70), breast (n = 56), pancreas (n = 46), and other organs (n = 402). Of the 19,106 participants, 14,916 had data on all five components of metabolic syndrome and gave rise to 687 cases of cancer death (including 201 cases of lung cancer). The numbers of participants with missing data for individual components are 2,992 for waist circumference, 2,704 for triglycerides, 2,783 for HDL cholesterol, 2,168 for systolic blood pressure, and 2,907 for blood glucose.

In the NHANES III, subjects were recruited from the civilian, noninstitutionalized U.S. population using a stratified, multistage probability sampling strategy, and those who had a low income, were older (60 years of age), or were members of minority groups (African or Mexican Americans) were oversampled. The NCHS Institutional Review Board approved the survey protocols, and informed consent was obtained from all subjects. The present study was not reviewed by the Institutional Review Board of Indiana University as the data analyzed are de-identified and publicly accessible.

Data Collection

Data analyzed in this paper were collected using standardized household interviews and health examinations [24]. A home interview was conducted and then followed by an extensive physical examination and blood collection at a mobile examination center. Self-reported information, including demographic, socioeconomic, and anthropometric characteristics as well as medical conditions and medications, were gathered using validated questionnaires during the home interview [24]. Metabolic syndrome was diagnosed according to the criteria of the National Cholesterol Education Program, which have been described in the Introduction of this paper. The individual components of metabolic syndrome [i.e. waist circumference, blood pressure, serum triglycerides, serum HDL cholesterol, and serum glucose] were measured using standard protocols or well-established methods during the physical examination. Specifically, waist circumference was determined at the iliac crest after a normal exhalation of breath. Systolic blood pressure (mmHg) was measured using a mercury sphygmomanometer while subjects were in a seated position.

Three measurements were taken and averaged for each subject to minimize measurement error [24]. Fasting blood samples were drawn by trained phlebotomists and were kept in freezers until time of analysis [24]. Serum concentrations of triglycerides and HDL cholesterol were measured enzymatically with Hitachi 704 Analyzer, while serum levels of glucose was determined using the glucose hexokinase method with Hitachi 737 Analyzer [24].

Statistical Analysis

Means (standard deviations) and percentages were calculated to show differences in the characteristics of study subjects by the number of abnormal metabolic syndrome components. Cox proportional hazards regression was used to estimate the hazard ratios (HR) and 95% confidence intervals (CI) for total cancer mortality, lung cancer mortality, and non-lung cancer mortality in relation to presence of metabolic syndrome, each of its individual components, and a composite score. Anatomic site-specific analysis was carried out only for lung cancer due to its relatively large sample size (n=201). Each of the individual components was examined by both dividing all subjects into quartiles and using its cut-off point specified in the Introduction section. HRs and 95% CIs were calculated with subjects who were in the lowest quartile (or whose value is less than the cut-off point) as the reference group, except HDL cholesterol for which the reference group were those who were in the highest quartile (or whose value is more than or equal to the cut-off point). The composite score has a range of 0–5, with 0 indicating no abnormal metabolic syndrome components and 1–5 representing the presence of 1–5 abnormal components, respectively. Based on the diagnosis criteria of metabolic syndrome, subjects with the composite score of 3, 4, or 5 were classified as having this metabolic disorder.

Selecting potential confounders was largely based on their relevance to metabolic syndrome and cancer risk [9]. The variables were adjusted as confounders in the regression models if they altered parameter estimates by 10% and/or had a p-value (<0.25) for their regression coefficients [25]. The multivariable models were adjusted for age (years), gender, race (non-Hispanic White, non-Hispanic Black, Mexican American, and other race), education (no education, less than high school, high school, college and graduate education), cigarette smoking (never, former, and current), alcohol intake (never, 1–2 drinks/day, 3–4 drinks/day or >4 drinks per day), and use of insulin (or diabetes), hypertension, and cholesterol-lowering medications (yes or no for each of the medications). Potential interactions of gender with each of individual metabolic syndrome components and its composite score were evaluated because gender differences in metabolic syndrome have been reported previously [26]. As none of the interactions tested was statistically significant, data analysis was not stratified by gender. Tests for linear trend across the quartiles of each component of metabolic syndrome or the four categories of its composite score were performed by including in the models an ordinal variable representing the median value of each quartile or category. A weight statement with a weight variable (WTPFEX6) was included in all analytical procedures to account for complex survey design, survey non-response, and post-stratification [27]. As the present study focused on metabolic syndrome, all of our data analysis was confined to the 14,916 subjects with complete data on this metabolic disorder.

All statistical analyses were conducted using SAS (version 9.3). All tests were two-sided and a p-value of <0.05 was considered statistically significant.

Results

The characteristics of study subjects are summarized in Table 1. Metabolic syndrome was present among 4,448 (29.8%) of 14,916 subjects. Subjects who were diagnosed with metabolic syndrome were more likely to be older, Mexican-American, and less educated. As expected, waist circumference, systolic blood pressure, and serum concentrations of triglycerides and glucose increased but serum concentrations of HDL cholesterol decreased with an increasing number of abnormal metabolic syndrome components.

Risk estimates described below are for subjects of all ages and both sexes. Results of total cancer mortality, lung cancer mortality, and non-lung cancer mortality in relation to metabolic syndrome as a single entity and the number of its individual components are displayed in Table 2. Individuals who developed metabolic syndrome had a 33% elevated total cancer mortality compared to those who were free from this abnormal health condition (HR, 1.33; 95% CI: 1.11–1.59). Of note, the risk of death from total cancer increased with an increasing number of abnormal metabolic syndrome components (p for trend = 0.0003). Specifically, compared with subjects who had 0–2 abnormal components, those who had 3, 4, and 5 abnormal components exhibited a 28%, 24%, and 87% increased risk of death from total cancer, respectively.

Results of individual metabolic syndrome components in relation to total cancer mortality, lung cancer mortality, and non-lung cancer mortality are shown in Table 3. After adjustment for confounders, systolic blood pressure and serum glucose were associated with an increased risk of death from total cancer [HR (95% CI) for highest vs. lowest quartiles: 1.67 (1.19–2.33), p-trend =0.002 and 1.34 (1.04–1.74), p-trend = 0.003, respectively]. There was a positive but borderline significant association between waist circumference and total cancer mortality [HR (95% CI) for highest vs. lowest quartiles: 1.32 (0.98–1.77), p-trend = 0.05]. Overall, serum triglycerides was positively and serum HDL cholesterol was inversely associated with total cancer mortality, but these associations did not have significant trends across quartiles. When these components were analyzed as dichotomous variables based on their respective cut-off points for defining metabolic syndrome, waist circumference, systolic blood pressure, HDL cholesterol, and serum glucose were associated with an increased risk of death from total cancer (Table 4).

Tables 2, 3, and 4 show no significant associations of metabolic syndrome and its individual components (except systolic blood pressure) with lung cancer mortality. The results for non-lung cancer mortality are largely similar to those for total cancer mortality, but the effects of metabolic syndrome and its components generally are somewhat larger on the former than on the latter (Tables 2 and 4). There is a monotonic upward trend for the association between number of abnormal components and non-lung cancer mortality [HR (95% CI) for 0–2 (reference) vs. 3, 4, and 5 components: 1.30 (0.98–1.73), 1.36 (0.98–1.88), and 2.68 (1.80–3.98), p-trend <.0001] (Table 2).

Discussion

The present study found statistically significant associations of all five individual metabolic syndrome components with total cancer mortality. The presence of metabolic syndrome as a whole is associated with a 33% elevated risk of death from total cancer. Furthermore, this promoting effect on total cancer mortality increased with an increasing number of abnormal metabolic syndrome components.

A number of epidemiologic studies have investigated the associations of metabolic syndrome and its components with the risk of developing cancer [10, 11]. Specifically, metabolic syndrome and its components have been associated with an increased mortality from cancers of the prostate [28, 29], breast [30–32], bone marrow (leukemia) [33], pancreas [33, 34], colon [35, 36], liver [34], and other sites of the digestive system [37]. It is well recognized that most cancer deaths occur among patients diagnosed with aggressive, advanced or metastatic cancer, a clinically important phenotype in contrast to a less impactful form of indolent, localized cancer. Therefore, evaluating risk factors in relation to cancer mortality is more relevant to the elucidation of the etiology of biologically aggressive cancer as numerous cases of cancer with little or no potential to progress to clinical significant stage have been diagnosed following screening tests (e.g. prostate and breast cancer) [38]. However, relatively few epidemiologic studies have evaluated the influence of metabolic syndrome and its components on the mortality of total cancer and site-specific cancers. The present study revealed that metabolic syndrome was associated with an increased risk of death from total cancer among a representative sample of the U.S. population, which is consistent with the results of a Korean cohort study (RR, 1.41; 95% CI, 1.08–1.84) carried out among 42,336 men and 32,168 women [18].

Besides analysis of metabolic syndrome as a single entity, examining its individual components and their combinations may shed new light on the role of this metabolic disorder in carcinogenesis. In the present study, we found that subjects who were in the highest quartile of systolic blood pressure and serum glucose experienced a significantly higher risk of total cancer mortality than those in the respective lowest quartiles (all p values for trend were <0.05). These results were in agreement with those of most previous studies [18, 20, 22, 39–41]. We also observed increased total cancer mortality in subjects with high serum triglycerides or low HDL cholesterol. However, risk estimates were statistically significant only for subjects who were in the third quartile of triglycerides or HDL cholesterol (p for trend for each of them was >0.05). In addition, given inconsistent associations between blood lipids and cancer risk across epidemiologic studies [42] and lack of the dose-response relations, chance findings for serum triglycerides and HDL cholesterol could not be entirely ruled out. Of note, the aforementioned results of metabolic syndrome components that were evaluated in quartiles were largely confirmed by the analysis that used their respective cut-off points for defining this adverse health condition. It is worth emphasizing that the present study revealed that the risk of total cancer mortality and particularly non-lung cancer mortality increased with an increasing number of metabolic syndrome components in a dose-response manner, suggesting a synergistic effect of these individual risk factors. This strategy of data analysis was not employed in most previous studies on metabolic syndrome.

There are some potential biological mechanisms by which metabolic syndrome modulates cancer risk. Metabolic syndrome prevalence has been rising as a consequence of upward trends in prevalence of overweight and obesity during the last few decades worldwide. Obesity (particularly central and visceral obesity) has been associated with insulin resistance and elevated insulin-like growth factor 1 (IGF-1) [43, 44]. Adipose tissue is an important source of estrogen in postmenopausal women among whom most cases of breast cancer occur [45]. Circulating estrogen concentrations are elevated among overweight and obese individuals probably because obesity-related inflammation induces the expression of cyclooxygenase-2 that consequently leads to enhanced aromatase expression and estrogen synthesis [44, 46, 47]. Considering that insulin, IGF-1, and estrogen have been identified as risk factors for breast and other common cancers [48, 49], it is thereby reasonable to infer that obesity promotes carcinogenesis at least in part through obesity-initiated metabolic syndrome.

Metabolic syndrome may also alter cancer risk through its critical role in type 2 diabetes mellitus and chronic systematic information induced by obesity. Obesity is an established risk factor for both diabetes and some sites of cancer [50]. Substantial evidence indicates that metabolic syndrome is a strong predictor of diabetes [51]. Furthermore, most epidemiologic studies conducted in diverse populations have shown that diabetes is associated with an increased risk of the cancers of the endometrium, pancreas, liver, colon, rectum, breast, and urinary bladder [50, 51], although reverse causality could account in part for the association between diabetes and pancreatic cancer risk [50]. Obesity has been consistently linked to chronic inflammation, which leads to changes in the tissue microenvironment that facilitate cancer initiation, progression, and metastasis [52]. In obesity, pro-inflammatory cytokines, such as interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α, are released from macrophages resident in adipose tissue, and these inflammatory mediators stimulate tumor growth and inhibit DNA repair mechanisms [51, 52].

The strengths of the present study include that the effect of metabolic syndrome on total cancer mortality was investigated in a prospective cohort study that was based on a national representative sample of the U.S. population. All five anthropometric, physiological, or biochemical components of metabolic syndrome were objectively measured with validated assessment tools or experimental methods. Therefore the data collected for these exposures are free from recall bias, which is frequently present in questionnaire-based exposure assessment. All potential confounders were tested and adjusted as appropriate for the associations of interest. More importantly, metabolic syndrome as a whole, its individual components, and their combinations were evaluated in relation to the risk of total cancer mortality, lung cancer mortality and non-lung cancer mortality in our data analysis.

Some limitations exist in the present study. The components of metabolic syndrome were measured only once, and therefore the effect of changes in these risk factors over time on total cancer risk could not be evaluated. Measurement errors for the five metabolic syndrome components, if non-differential, are likely to lead to attenuated risk estimate of their associations with cancer mortality. As in other observational studies, it is possible that residual confounding due to unmeasured or inaccurately measured confounders might have

somewhat distorted the results obtained from the present study. Metabolic syndrome and its components in relation to site-specific cancers were not examined due to small sample size (described in Materials and Methods). Of all sites of cancer, lung cancer contributed to the largest number of deaths (n=201) in the present study. We examined metabolic syndrome and its components in relation to lung cancer mortality but did not identify overall apparent effects. It is intriguing to observe that the dose-response relation with the number of the abnormal components of metabolic syndrome is more pronounced and statistically significant for non-lung cancer mortality than for total cancer mortality, which may be in part ascribed to its overall null results with lung cancer mortality.

In summary, metabolic syndrome and its individual components are associated with an increased risk of total cancer mortality and non-lung cancer mortality. The findings of the present study offer novel evidence for the potential role of metabolic syndrome in carcinogenesis and mechanistic data for the associations between obesity and cancer risk. If the results of this study are confirmed in other well-conducted case-control and particularly prospective cohort studies, the public health importance of maintaining healthy levels of the components of the metabolic syndrome would be accentuated. This strategy is expected to result in a tremendous reduction in cancer incidence and mortality attributable to the global epidemic of obesity and subsequent metabolic syndrome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Torre LA, Bray F, Sigel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015; 65:5–29. DOI: 10.3322/caac.21262 [PubMed: 25559415]

2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015; 65:5–29. DOI: 10.3322/caac.21254 [PubMed: 25559415]

3. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet. 2011; 377:557–567. DOI: 10.1016/S0140-6736(10)62037-5 [PubMed: 21295846]

4. Ligibel JA, Alfano CM, Courneya KS, Demark-Wahnefried W, Burger RA, Chlebowski RT, Fabian CJ, et al. American Society of Clinical Oncology position statement on obesity and cancer. J Clin Oncol. 2014; 32:3568–3574. DOI: 10.1200/JCO.2014.58.4680 [PubMed: 25273035]

5. Demark-Wahnefried W, Platz EA, Ligibel JA, Blair CK, Courneya KS, Meyerhardt JA, Ganz PA, et al. The role of obesity in cancer survival and recurrence. Cancer Epidemiol Biomarkers Prev. 2012; 21:1244–1259. DOI: 10.1158/1055-9965.EPI-12-0485 [PubMed: 22695735]

6. Goodwin PJ, Stambolic V. Impact of the obesity epidemic on cancer. Annu Rev Med. 2015; 66:281–296. DOI: 10.1146/annurev-med-051613-012328 [PubMed: 25423596]

7. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120:1640–1645. DOI: 10.1161/CIRCULATIONAHA.109.192644 [PubMed: 19805654]

8. McCullough AJ. Epidemiology of the metabolic syndrome in the USA. J Dig Dis. 2011; 12:333–340. DOI: 10.1111/j.1751-2980.2010.00469.x [PubMed: 21091931]

9. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994. Arch Intern Med. 2003; 163:427–436. DOI: 10.1001/archinte.163.4.427 [PubMed: 12588201]

10. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Rafaniello C, Panagiotakos DB, et al. Colorectal cancer association with metabolic syndrome and its components: a systematic review with meta-analysis. Endocrine. 2013; 44:634–647. DOI: 10.1007/s12020-013-9939-5 [PubMed: 23546613]

11. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Rafaniello C, Giugliano D. Metabolic syndrome and postmenopausal breast cancer: systematic review and meta-analysis. Menopause. 2013; 20:1301–1309. DOI: 10.1097/GME.0b013e31828ce95d [PubMed: 23571527]

12. Teucher B, Rohrmann S, Kaaks R. Obesity: focus on all-cause mortality and cancer. Maturitas. 2010; 65:112–116. DOI: 10.1016/j.maturitas.2009.11.018 [PubMed: 20022719]

13. Golabek T, Bukowczan J, Chlosta P, Powroznik J, Dobruch J, Borowka A. Obesity and prostate cancer incidence and mortality: a systematic review of prospective cohort studies. Urol Int. 2014; 92:7–14. DOI: 10.1159/000351325 [PubMed: 23942223]

14. Dal Maso L, Zucchetto A, Talamini R, Serraino D, Stocco CF, Vercelli M, Falcini F, et al. Effect of obesity and other lifestyle factors on mortality in women with breast cancer. Int J Cancer. 2008; 123:2188–2194. DOI: 10.1002/ijc.23747 [PubMed: 18711698]

15. Adami HO, Trichopoulos D. Obesity and mortality from cancer. N Engl J Med. 2003; 348:1623–1624. DOI: 10.1056/NEJMp030029 [PubMed: 12711736]

16. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003; 348:1625–1638. DOI: 10.1056/NEJMoa021423 [PubMed: 12711737]

17. Jaggers JR, Sui X, Hooker SP, LaMonte MJ, Matthews CE, Hand GA, Blair SN. Metabolic syndrome and risk of cancer mortality in men. Eur J Cancer. 2009; 45:1831–1838. DOI: 10.1016/j.ejca.2009.01.031 [PubMed: 19250819]

18. Lee JS, Cho SI, Park HS. Metabolic syndrome and cancer-related mortality among Korean men and women. Ann Oncol. 2010; 21:640–645. DOI: 10.1093/annonc/mdp344 [PubMed: 19759188]

19. Stocks T, Van Hemelrijck M, Manjer J, Bjorge T, Ulmer H, Hallmans G, Lindkvist B, et al. Blood pressure and risk of cancer incidence and mortality in the Metabolic Syndrome and Cancer Project. Hypertension. 2012; 59:802–810. DOI: 10.1161/HYPERTENSIONAHA.111.189258 [PubMed: 22353615]

20. Seidell JC. Waist circumference and waist/hip ratio in relation to all-cause mortality, cancer and sleep apnea. Eur J Clin Nutr. 2010; 64:35–41. DOI: 10.1038/ejcn.2009.71 [PubMed: 19639001]

21. Nago N, Ishikawa S, Goto T, Kayaba K. Low cholesterol is associated with mortality from stroke, heart disease, and cancer: the Jichi Medical School Cohort Study. J Epidemiol. 2011; 21:67–74. DOI: 10.2188/jea.JE20100065 [PubMed: 21160131]

22. Parekh N, Lin Y, Hayes RB, Albu JB, Lu-Yao GL. Longitudinal associations of blood markers of insulin and glucose metabolism and cancer mortality in the third National Health and Nutrition Examination Survey. Cancer Causes Control. 2010; 21:631–642. DOI: 10.1007/s10552-009-9492-y [PubMed: 20094767]

23. Center for Disease Control and Prevention. National health and nutrition examination survey data. Hyattsville, MD: National Centerf for Health Statistics; 2016. Website- http://www.cdc.gov/nchs/nhanes/about_nhanes.htm [Accessed January 2016]

24. Center for Disease Control and Prevention. Plan and operation of the third national health and nutrition examination survey, 1988–94. Series 1: programs and collection procedures. Vital Health Stat. 1994; 1(32):1–407.

25. Bursac Z, Gauss H, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code for Biology and Medicine. 2008; 3doi: 10.1186/1751-0473-3-17

26. Beigh SH, Jain S. Prevalence of metabolic syndrome and gender differences. Bioinformation. 2012; 8:613–616. DOI: 10.6026/97320630008613 [PubMed: 22829741]

27. Nation Center for Health Statistics. Analytic and reporting guidelines: the third national health and nutrition examination survey, NHANES III (1988–94). Vol. 2015. Center for Disease Control and Prevention (CDC); 1996.

28. Grundmark B, Garmo H, Loda M, Busch C, Holmberg L, Zethelius B. The metabolic syndrome and the risk of prostate cancer under competing risks of death from other causes. Cancer Epidemiol Biomarkers Prev. 2010; 19:2088–2096. DOI: 10.1158/1055-9965.EPI-10-0112 [PubMed: 20647401]

29. Xiang YZ, Xiong H, Cui ZL, Jiang SB, Xia QH, Zhao Y, Li GB, et al. The association between metabolic syndrome and the risk of prostate cancer, high-grade prostate cancer, advanced prostate cancer, prostate cancer-specific mortality and biochemical recurrence. J Exp Clin Cancer Res. 2013; 32:9.doi: 10.1186/1756-9966-32-9 [PubMed: 23406686]

30. Bjorge T, Lukanova A, Jonsson H, Tretli S, Ulmer H, Manjer J, Stocks T, et al. Metabolic syndrome and breast cancer in the me-can (metabolic syndrome and cancer) project. Cancer Epidemiol Biomarkers Prev. 2010; 19:1737–1745. DOI: 10.1158/1055-9965.EPI-10-0230 [PubMed: 20615887]

31. Emaus A, Veierod MB, Tretli S, Finstad SE, Selmer R, Furberg AS, Bernstein L, et al. Metabolic profile, physical activity, and mortality in breast cancer patients. Breast Cancer Res Treat. 2010; 121:651–660. DOI: 10.1007/s10549-009-0603-y [PubMed: 19882245]

32. Lopez-Saez JB, Martinez-Rubio JA, Alvarez MM, Carrera CG, Dominguez Villar M, de Lomas Mier AG, Domenech C, et al. Metabolic profile of breast cancer in a population of women in southern Spain. Open Clin Cancer J. 2008; 2:1–6. DOI: 10.2174/1874189400802010001 [PubMed: 18665244]

33. Batty GD, Shipley MJ, Marmot MG, Davey Smith G, Whitehall S. Blood pressure and site-specific cancer mortality: evidence from the original Whitehall study. Br J Cancer. 2003; 89:1243–1247. DOI: 10.1038/sj.bjc.6601255 [PubMed: 14520454]

34. Batty GD, Shipley MJ, Marmot M, Smith GD. Diabetes status and post-load plasma glucose concentration in relation to site-specific cancer mortality: findings from the original Whitehall study. Cancer Causes Control. 2004; 15:873–881. DOI: 10.1007/s10552-004-1050-z [PubMed: 15577289]

35. Colangelo LA, Gapstur SM, Gann PH, Dyer AR, Liu K. Colorectal cancer mortality and factors related to the insulin resistance syndrome. Cancer Epidemiol Biomarkers Prev. 2002; 11:385–391. [PubMed: 11927499]

36. Trevisan M, Liu J, Muti P, Misciagna G, Menotti A, Fucci F, Risk F, et al. Markers of insulin resistance and colorectal cancer mortality. Cancer Epidemiol Biomarkers Prev. 2001; 10:937–941. [PubMed: 11535544]

37. Matthews CE, Sui X, LaMonte MJ, Adams SA, Hebert JR, Blair SN. Metabolic syndrome and risk of death from cancers of the digestive system. Metabolism. 2010; 59:1231–1239. DOI: 10.1016/j.metabol.2009.11.019 [PubMed: 20045534]

38. Marcus PM, Prorok PC, Miller AB, DeVoto EJ, Kramer BS. Conceptualizing overdiagnosis in cancer screening. J Natl Cancer Inst. 2015; 107doi: 10.1093/jnci/djv014

39. Grossman E, Messerli FH, Boyko V, Goldbourt U. Is there an association between hypertension and cancer mortality? Am J Med. 2002; 112:479–486. DOI: 10.1016/S0002-9343(02)01049-5 [PubMed: 11959059]

40. Dankner R, Shanik MH, Keinan-Boker L, Cohen C, Chetrit A. Effect of elevated basal insulin on cancer incidence and mortality in cancer incident patients: the Israel GOH 29-year follow-up study. Diabetes Care. 2012; 35:1538–1543. DOI: 10.2337/dc11-1513 [PubMed: 22619079]

41. Perseghin G, Calori G, Lattuada G, Ragogna F, Dugnani E, Garancini MP, Crosignani P, et al. Insulin resistance/hyperinsulinemia and cancer mortality: the Cremona study at the 15th year of follow-up. Acta Diabetol. 2012; 49:421–428. DOI: 10.1007/s00592-011-0361-2 [PubMed: 22215126]

42. Radisauskas R, Kuzmickiene I, Milinaviciene E, Everatt R. Hypertension, serum lipids and cancer risk: A review of epidemiological evidence. Medicina (Kaunas). 2016; 52:89–98. org/10.1016/j.medici.2016.03.002. [PubMed: 27170481]

43. Doyle SL, Donohoe CL, Lysaght J, Reynolds JV. Visceral obesity, metabolic syndrome, insulin resistance and cancer. Proc Nutr Soc. 2012; 71:181–189. DOI: 10.1017/S002966511100320X [PubMed: 22051112]

44. Gallagher EJ, LeRoith D. Epidemiology and molecular mechanisms tying obesity, diabetes, and the metabolic syndrome with cancer. Diabetes Care. 2013; 36(Suppl 2):S233–239. DOI: 10.2337/dcS13-2001 [PubMed: 23882051]

45. Suzuki R, Saji S, Toi M. Impact of body mass index on breast cancer in accordance with the life-stage of women. Front Oncol. 2012; 2:123.doi: 10.3389/fonc.2012.00123 [PubMed: 23061041]

46. Simpson E, Brown KA. Obesity and breast cancer: role of inflammation and aromatase. J Mol Endocrinol. 2013; doi: 10.1530/JME-13-0217

47. Hursting SD, Hursting MJ. Growth signals, inflammation, and vascular perturbations: mechanistic links between obesity, metabolic syndrome, and cancer. Arterioscler Thromb Vasc Biol. 2012; 32:1766–1770. DOI: 10.1161/ATVBAHA.111.241927 [PubMed: 22815342]

48. Sridhar SS, Goodwin PJ. Insulin-insulin-like growth factor axis and colon cancer. J Clin Oncol. 2009; 27:165–167. DOI: 10.1200/JCO.2008.19.8937 [PubMed: 19064959]

49. Belardi V, Gallagher EJ, Novosyadlyy R, Leroith D. Insulin and IGFs in Obesity-Related Breast Cancer. J Mammary Gland Biol Neoplasia. 2013; doi: 10.1007/s10911-013-9303-7

50. Klil-Drori AJ, Azoulay L, Pollak MN. Cancer, obesity, diabetes, and antidiabetic drugs: is the fog clearing? Nat Rev Clin Oncol. 2016; 2016doi: 10.1038/nrclinonc.2016.120

51. Hua F, Yu JJ, Hu ZW. Diabetes and cancer, common threads and missing links. Cancer Lett. 2016; 374:54–61. DOI: 10.1016/j.canlet.2016.02.006 [PubMed: 26879686]

52. Hoenerhoff MJ. Inflammation and cancer: Partners in crime. Vet J. 2015; 206:1–2. DOI: 10.1016/j.tvjl.2015.07.007 [PubMed: 26324636]

53. Younossi ZM, Zheng L, Stepanova M, Venkatesan C, Mir HM. Moderate, excessive or heavy alcohol consumption: each is significantly associated with increased mortality in patients with chronic hepatitis C. Aliment Pharmacol Ther. 2013; 37:703–709. DOI: 10.1111/apt.12265 [PubMed: 23432436]

Table 1

Baseline characteristics of 14,916 participants by the number of abnormal metabolic syndrome components in the Third National Health and Nutrition Examination Survey, 1988–1994

Characteristics	No. of abnormal metabolic syndrome components			
	0–2 (n=10,468)	3 (n=2,452)	4 (n=1,460)	5 (n=536)
	Mean (SD)			
Age (year)	39.7 (18)	50.4 (18)	56.2 (16)	61.6 (13)
Waist circumference (cm)	87.0 (13)	102.1(12)	107.7(12)	109.3 (11)
Systolic blood pressure (mmHg)	117.2 (17)	131.0 (20)	137.3 (19)	146.1 (15)
Serum triglycerides (mg/dl)	108.8 (66)	204 (132)	246.0 (130)	289 (155)
Serum HDL cholesterol (mg/dl)	53.5 (15)	43.5 (13)	39.7 (11)	36.6 (7)
Serum glucose (mg/dl)	90.4 (21)	104 (44)	117 (55)	151.4 (71)
	N (%)[a]			
Sex				
Male	5122 (74.5)	1151 (14.5)	669 (8.6)	204 (2.3)
Female	5346 (75.3)	1301 (14.0)	791 (7.7)	332 (3.0)
Race				
Non-Hispanic White	4107 (74.0)	1055 (14.5)	706 (8.5)	282 (3.0)
Non-Hispanic Black	3086 (78.5)	585 (13.4)	284 (6.4)	85 (1.8)
Mexican-American	2822 (73.5)	722 (16.0)	419 (8.1)	157 (2.5)
Other race	453 (79.6)	90 (12.1)	51 (7.0)	12 (1.2)
Education[b]				
Never been to school	192 (65.6)	86 (16.8)	74 (11.4)	32 (6.2)
Less than High school	1819 (61.3)	610 (19.6)	417 (14.4)	169 (4.7)
High school education	5133 (73.0)	1160 (14.8)	667 (9.1)	244 (3.2)
College education	2645 (80.6)	477 (12.4)	236 (5.3)	73 (1.7)
Graduate education	613 (80.6)	108 (11.7)	62 (6.3)	17 (1.4)
Cigarette Smoking				
Never	5398 (71.9)	1136 (15.1)	706 (9.4)	265 (3.5)
Former	2884 (75.3)	597 (15.6)	269 (7.0)	78 (2.0)
Current	2186 (61.0)	719 (20.1)	485 (13.5)	193 (5.4)
Alcohol Consumption[c]				
No alcohol	4870 (67.9)	1458 (17.1)	945 (11.0)	378 (4.0)
1–2 drinks/day	5295 (80.1)	942 (12.2)	494 (6.0)	149 1.7)
3–4 drinks/day	235 (84.6)	38 (9.5)	15 (4.5)	4 (1.4)
>4 drinks/day	68 (86.9)	14 (6.7)	6 (2.9)	5 (3.4)

[a] Percentages were calculated by using sample weights to report estimates that would be representative of the U.S. population.

[b] Eighty-two participants had missing data on education.

[c] In the NHANES, one drink was defined as 10 gram pure ethanol that is equivalent to 12 ounces of beer, 4 ounces of wine or 1 ounce of hard liquor [53].

Table 2

Hazard ratios (HR) with 95% confidence intervals (CI) for total cancer mortality, lung cancer mortality, and non-lung cancer mortality in relation to metabolic syndrome and the number of abnormal components among 14,916 participants in the National Health and Nutrition Examination Survey, 1988–2006

	Number of Subjects (%)	Number of Cancer Deaths	Total Cancer Mortality HR (95% CI) n=687		Lung Cancer Mortality HR (95% CI) n=201		Non-Lung Cancer Mortality HR (95% CI) n=486	
			Age-Adjusted	Multivariable-Adjusted [a]	Age-Adjusted	Multivariable-Adjusted [a]	Age-Adjusted	Multivariable-Adjusted [a]
Presence of metabolic syndrome								
No	10,468 (70.2%)	372	Reference	Reference	Reference	Reference	Reference	Reference
Yes	4,448 (29.8%)	315	1.31 (1.10–1.57)	1.33 (1.11–1.59)	1.11 (0.82–1.49)	1.05 (0.77–1.43)	1.44 (1.15–1.80)	1.46 (1.15–1.84)
No. of abnormal metabolic syndrome components								
0–2	10,468 (70.2%)	372	Reference	Reference	Reference	Reference	Reference	Reference
3	2,452 (16.4%)	163	1.29 (1.04–1.59)	1.28 (1.03–1.59)	1.22 (0.85–1.73)	1.13 (0.79–1.62)	1.31 (0.99–1.73)	1.30 (0.98–1.73)
4	1,460 (9.8%)	102	1.21 (0.94–1.56)	1.24 (0.96–1.60)	1.03 (0.67–1.60)	0.95 (0.61–1.50)	1.31 (0.95–1.80)	1.36 (0.98–1.88)
5	536 (3.6%)	50	1.68 (1.22–2.32)	1.87 (1.34–2.63)	0.88 (0.44–1.77)	0.90 (0.44–1.86)	2.36 (1.61–3.44)	2.68 (1.80–3.98)
p for trend				0.0003		0.96		<.0001

[a] Adjusted for age (years), gender, race (non-Hispanic white, non-Hispanic black, Mexican American, and other race), education (no education, less than high school, high school, college education, and graduate education), cigarette smoking (current, former, and never), alcohol intake (yes or no), and use of insulin or diabetes, hypertension, and cholesterol-lowering medications (yes or no for each of the medications).

Table 3

Hazard ratios (HR) with 95% confidence intervals (CI) for total cancer mortality, lung cancer mortality, and non-lung cancer mortality by quartiles of components of metabolic syndrome among 14,916 participants in the National Health and Nutrition Examination Survey, 1988–2006

Components[a]	No. of Cancer Deaths	Person-Years	Total Cancer Mortality HR (95% CI)[a] n=687		Lung Cancer Mortality HR (95% CI)[a] n=201		Non-Lung Cancer Mortality HR (95% CI)[a] n=486	
			Age-Adjusted	Multivariable-Adjusted	Age-Adjusted	Multivariable-Adjusted	Age-Adjusted	Multivariable-Adjusted
Waist circumference (cm)								
Q1 (≤82.1)	105	52,577	Reference	Reference	Reference	Reference	Reference	Reference
Q2 (82.2–92.1)	150	51,014	1.21 (0.90–1.62)	1.12 (0.83–1.51)	1.49 (0.94–2.38)	1.24 (0.77–2.00)	1.10 (0.75–1.62)	1.04 (0.70–1.55)
Q3 (92.2–102.1)	204	49,153	1.31 (0.98–1.74)	1.18 (0.88–1.58)	1.30 (0.81–2.08)	1.04 (0.64–1.70)	1.27 (0.87–1.83)	1.15 (0.79–1.68)
Q4 (≥102.2)	228	48,771	**1.52 (1.15–2.01)**	1.32 (0.98–1.77)	1.28 (0.80–2.04)	0.89 (0.54–1.47)	**1.57 (1.10–2.24)**	1.42 (0.97–2.07)
p for trend				**0.05**		0.30		**0.03**
Systolic blood pressure (mmHg)								
Q1 (≤111)	60	56,142	Reference	Reference	Reference	Reference	Reference	Reference
Q2 (112–121)	106	52,163	1.33 (0.95–1.87)	1.19 (0.85–1.68)	**1.92 (1.08–3.39)**	1.63 (0.91–2.91)	0.99 (0.64–1.53)	0.91 (0.58–1.41)
Q3 (122–135)	165	49,801	1.32 (0.95–1.84)	1.17 (0.84–1.63)	1.72 (0.97–3.05)	1.46 (0.82–2.60)	1.00 (0.66–1.51)	0.90 (0.59–1.38)
Q4 (≥136)	356	43,409	**1.80 (1.29–2.51)**	**1.67 (1.19–2.33)**	**2.29 (1.28–4.09)**	**2.16 (1.21–3.86)**	**1.51 (1.00–2.27)**	1.38 (0.91–2.10)
p for trend				**0.002**		**0.009**		**0.005**
Serum triglycerides (mg/dl)								
Q1 (≤77)	109	52,026	Reference	Reference	Reference	Reference	Reference	Reference
Q2 (78–111)	158	51,718	**1.35 (1.01–1.82)**	1.29 (0.96–1.73)	1.24 (0.76–2.11)	1.05 (0.64–1.71)	1.39 (0.95–2.05)	1.39 (0.94–2.04)
Q3 (112–167)	224	49,100	**1.55 (1.16–2.05)**	**1.45 (1.09–1.94)**	**1.85 (1.18–2.91)**	1.50 (0.95–2.36)	1.25 (0.85–1.82)	1.24 (0.85–1.82)
Q4 (≥168)	196	48,672	1.12 (0.84–1.51)	1.07 (0.79–1.45)	0.82 (0.50–1.37)	0.67 (0.40–1.13)	1.27 (0.87–1.85)	1.28 (0.87–1.88)
p for trend				0.88		0.27		0.53
Serum HDL cholesterol (mg/dl)								
Q1 (≤40)	203	50,462	**1.38 (1.09–1.74)**	1.17 (0.91–1.51)	**1.56 (1.06–2.32)**	0.94 (0.61–1.45)	**1.39 (1.03–1.87)**	1.36 (0.98–1.90)
Q2 (41–48)	170	48,421	**1.40 (1.11–1.78)**	**1.29 (1.01–1.65)**	1.37 (0.91–2.08)	1.03 (0.67–4.58)	**1.40 (1.04–1.88)**	**1.39 (1.02–1.90)**
Q3 (49–58)	139	50,755	0.92 (0.71–1.20)	0.90 (0.69–1.17)	1.14 (0.74–1.75)	0.97 (0.63–1.51)	0.82 (0.58–1.15)	0.84 (0.59–1.18)
Q4 (≥59)	175	51,877	Reference	Reference	Reference	Reference	Reference	Reference
p for trend				**0.07**		0.84		**0.02**
Serum glucose (mg/dl)								

Components[a]	No. of Cancer Deaths	Person-Years	Total Cancer Mortality HR (95% CI)[a] n=687		Lung Cancer Mortality HR (95% CI)[a] n=201		Non-Lung Cancer Mortality HR (95% CI)[a] n=486	
			Age-Adjusted	Multivariable-Adjusted	Age-Adjusted	Multivariable-Adjusted	Age-Adjusted	Multivariable-Adjusted
Q1 (85)	102	55,271	Reference	Reference	Reference	Reference	Reference	Reference
Q2 (86–92)	144	53,938	0.96 (0.73–1.26)	0.97 (0.73–1.27)	0.72 (0.48–1.10)	0.74 (0.48–1.13)	1.14 (0.78–1.66)	1.15 (0.79–1.69)
Q3 (93–100)	159	45,430	0.85 (0.64–1.12)	0.87 (0.66–1.15)	0.62 (0.40–0.96)	0.65 (0.42–1.01)	1.03 (0.71–1.52)	1.06 (0.72–1.56)
Q4 (101)	282	45,877	1.35 (1.05–1.74)	1.34 (1.04–1.74)	0.86 (0.58–1.29)	0.84 (0.56–1.26)	1.82 (1.28–2.57)	1.83 (1.28–2.61)
p for trend				0.003		0.63		<.0001

[a] Adjusted for age (years), gender, race (non-Hispanic white, non-Hispanic black, Mexican American, and other race), education (no education, less than high school, high school, college education, and graduate education), cigarette smoking (current, former, and never), alcohol intake (yes or no), and use of insulin or diabetes, hypertension, and cholester ol-lowering medications (yes or no for each of the medications).

Table 4

Hazard ratios (HR) with 95% confidence intervals (CI) for total cancer mortality, lung cancer mortality, and non-lung cancer mortality by cut-off points of components of metabolic syndrome among 14,916 participants in the National Health and Nutrition Examination Survey, 1988–2006

Components[a]	No. of Cancer Deaths	Person-Years	Total Cancer Mortality HR (95% CI)[a] n=687		Lung Cancer Mortality HR (95% CI)[a] n=201		Non-Lung Cancer Mortality HR (95% CI)[a] n=486	
			Age-Adjusted	Multivariable-Adjusted	Age-Adjusted	Multivariable-Adjusted	Age-Adjusted	Multivariable-Adjusted
Waist circumference								
<102cm men or <88cm women	349	119,552	Reference	Reference	Reference	Reference	Reference	Reference
102cm men or 88cm women	338	81,962	1.18 (0.99–1.41)	1.29 (1.08–1.55)	0.84 (0.62–1.12)	0.91 (0.67–1.23)	1.34 (1.06–1.68)	1.41 (1.11–1.79)
Systolic blood pressure								
<130 mmHg	262	141,295	Reference	Reference	Reference	Reference	Reference	Reference
130 mmHg	425	60,219	1.23 (1.01–1.49)	1.21 (1.00–1.47)	1.21 (0.87–1.67)	1.24 (0.90–1.72)	1.30 (1.02–1.66)	1.27 (0.99–1.62)
Serum triglycerides (mg/dl)								
<150 mg/dL	426	140,772	Reference	Reference	Reference	Reference	Reference	Reference
150 mg/dL	261	60,743	0.92 (0.77–1.10)	0.89 (0.74–1.07)	0.90 (0.67–1.22)	0.82 (0.60–1.11)	0.93 (0.74–1.17)	0.92 (0.73–1.17)
Serum HDL cholesterol (mg/dl)								
40 mg/dLmen/ 50mg/dl women	400	121,550	Reference	Reference	Reference	Reference	Reference	Reference
<40 mg/dLmen/<50mg/dl women	287	79,964	1.27 (1.07–1.51)	1.23 (1.03–1.47)	1.24 (0.94–1.66)	1.06 (0.79–1.42)	1.33 (1.07–1.66)	1.36 (1.08–1.71)
Serum glucose (mg/dl)								
<100 mg/dL	390	150,150	Reference	Reference	Reference	Reference	Reference	Reference
100 mg/dL	297	51,365	1.38 (1.16–1.65)	1.36 (1.13–1.63)	1.12 (0.82–1.52)	1.07 (0.78–1.47)	1.58 (1.26–1.97)	1.56 (1.24–1.97)

[a] Adjusted for age (years), gender, race (non-Hispanic white, non-Hispanic black, Mexican American, and other race), education (no education, less than high school, high school, college education, and graduate education), cigarette smoking (current, former, and never), alcohol intake (yes or no), and use of insulin or diabetes, hypertension, and cholesterol-lowering medications (yes or no for each of the medications).