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Original Article

Metabolic syndrome, obesity, and the risk of cancer development

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ABSTRACT

Background: Metabolic syndrome and its components are severe global health issues that are increasing in frequency as the prevalence of obesity increases. Various studies have established a correlation between metabolic syndrome and diseases including, diabetes mellitus, non-alcoholic fatty liver disease, cirrhosis, and cardiovascular disease. In recent years, correlations have also been detected between obesity and metabolic syndrome and the prevalence of certain types of cancer. The current study examines whether obesity and metabolic syndrome components are risk factors for cancer among the adult population in Israel.
Methods: A cohort study analysis was performed of 24,987 initially healthy men and women who underwent yearly medical assessments at the Institute for Medical Screening in the Sheba Medical Center. Data from the Institute for Medical Screening database was correlated with that from the Israel Cancer Center in the Ministry of Health updated to December 2013. The correlation between metabolic syndrome, obesity, and the overall risk of cancer as well as the risks of specific types of cancer were examined.
Results: Of 20,444 subjects for whom complete data were available, 1535 were diagnosed with cancer during the mean follow-up time of 104.3 months. In a multi-variant analysis, no significant correlation was found between metabolic syndrome or obesity and the incidence of cancer. When the data were stratified by gender and cancer type, however, a significant association between metabolic syndrome and breast cancer in women was observed ($P = 0.03$, $HR = 1.67$, 95% $CI = 1.05–2.67$).
Conclusion: Metabolic syndrome correlates with higher than expected breast cancer incidence in women.

1. Introduction

Obesity and metabolic syndrome contribute to cardiovascular morbidity and mortality [1]. In the US, nearly 35% of all adults and 50% of those aged 60 years or older are estimated to have metabolic syndrome [2], and 35% of adults aged 20 years or older are considered to be obese [3]. In Israel, 34% of adults are overweight, 16% are obese [4], and 20% have the metabolic syndrome [5]. Several studies have shown correlations between the prevalence of certain types of cancer and obesity and metabolic syndrome. In the Metabolic Syndrome and Cancer Project cohort, metabolic syndrome and a higher BMI were related to an increased risk of colorectal cancer [6]. In the same population, metabolic syndrome was associated with a decreased risk of breast cancer in women below age 50 with high body mass index and with an increased risk of breast cancer mortality in women above 60[7]. In the Surveillance, Epidemiology, and End Results (SEER) Medicare database, metabolic syndrome was significantly associated with increased risk of hepatocellular carcinoma [8].

The aim of the current study was to determine the relationship between the metabolic syndrome and high BMI and incidence of cancer (overall and specific types) in a cohort of healthy subjects in Israel undergoing a yearly medical examination.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; PSA, prostate-specific antigen; HDL, High-density lipoprotein.

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2. Methods

2.1. Patient cohort and clinical evaluation

We performed a retrospective cohort study of consecutive patients who underwent routine check-ups during the years 2000 through 2010 at The Institute for Medical Screening of the Chaim Sheba Medical Center. Chaim Sheba is a university-affiliated tertiary hospital that serves as Israel's national medical center in many fields. The Institute for Medical Screening of the Chaim Sheba Medical Center performs about 9000 annual examinations [9]. A computerized database established in the year 2000 was used as the source of data for the present study. All participants were asymptomatic subjects attending periodic health screening examinations as private individuals or as part of health executive programs. Each annual checkup included a structured medical history, physical examination, chest radiograph, stress test, occult blood test in stool and blood tests (including complete blood count, C-reactive protein (CRP), chemistry panel, lipid profile, and prostate-specific antigen (PSA) — in men over the age of 50). Further screening procedures (e.g. gastrointestinal endoscopy, screening breast imaging) are performed according to guidelines [10].

All participants were over the age of 18 years at the time of the first visit. Most were men with a higher than average socioeconomic status. Participants who had a confirmed diagnosis of a malignant disease at their first visit were excluded from the analysis. Participants with missing data for any one of the components of metabolic syndrome (BMI, blood pressure, fasting glucose levels, triglyceride levels, HDL-cholesterol levels) were excluded from the initial analysis. Metabolic syndrome was defined from data of the first visit of each subject, according to the ATP III criteria [11]. Since waist circumference was not measured, we used BMI as a measure of obesity, with a cutoff value of 30 kg/m^2. Overweight was defined as a BMI value higher than 25 kg/m^2.

The occurrence of cancer was verified using the Israel Ministry of Health Cancer Registry with data updated as of December 2013. The registry includes all cases of malignant diseases diagnosed in all hospitals in Israel since 1982, with the exceptions of non-melanoma skin cancers and leukemias. All cases are registered according to the International Classification of Diseases for Oncology, second edition (ICD-02). The study was approved by the Sheba Medical Center institutional review board.

2.2. Sample size

Incidence of cancer of the Israeli population was used to calculate the sample size. According to the Israel National Health Survey (2007–2010), the incidence of cancer in the adult population (above 21) is 0.32% [12]. In order to evaluate a hazard ratio of 1.5 at a significant level of 5% and power of 80%, 196 cancer events were needed.

2.3. Statistical analysis

Categorical variables were described using frequency, and percentage continuous variables were described using mean, standard deviation (SD), median, and inter-quartile range (IQR). Patients with missing values were compared to those with all parameters in order to exclude a selection bias. T-Test (for continuous variables) and Chi-square test (for categorical variable) were used for this purpose. The same tests were used to compare the baseline parameters of patients with and without metabolic syndrome. Analysis of variance (ANOVA) was used to compare age between BMI categories. The Scheffé method was used for post-hoc tests. Length of follow-up estimation was based on the reverse Kaplan–Meier method [13]. Kaplan–Meir curves and log-rank test were used to compare cancer incidence between patients with and without metabolic syndrome, as well as to compare incidence in patients in different BMI categories. Univariate Cox regressions were used to assess the crude associations between cancer incidence, metabolic syndrome, and BMI categories. Multivariate Cox regressions were used to evaluate the association adjusted for age and gender. All tests were two-sided. For all analyses, p values less than 0.05 were considered as statistically significant. SPSS software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) was used for all the statistical analyses.

3. Results

3.1. Patient cohort

The average age of the 24,987 participants included at baseline was 48.3 years (SD 10.9). Of the participants, 18,083 (72.4%) were men, and 6903 (27.6%) were women. Cancer was diagnosed in 1559 subjects. Twenty-four participants had a diagnosis of cancer at the first screening visit and were excluded. The mean length of follow-up was 104.3 months (95% CI: 103.7–104.8).

3.2. Metabolic syndrome and cancer incidence

Four thousand five hundred and forty-three subjects had data missing for at least one of the components necessary for metabolic syndrome diagnosis, and were excluded from the analysis. A flow chart detailing how the study cohort was selected is shown in Fig. 1. The excluded patients did not differ statistically from the general cohort in terms of age, gender, or levels of metabolic components for which data were available. Among the remaining 20,444 subjects, all-type malignancy was diagnosed in 1175 final participants (5.7%). The percentages of each specific cancer-type are depicted in Fig. 2 and summarized by gender in Table 1. The most prevalent cancers were prostate (21%), breast (12%), and melanoma (11%).

Among the 20,444 participants with complete data, the age ranged from 25 to 91 years (average age 47.4, SD 12.2). Of these 14,913 (72.9%) were men, and 5531 (27.1%) were women. The prevalence of the various components of metabolic syndrome at first visit is summarized in Table 2. At least three components of metabolic syndrome were found in 3202 (15.7%) subjects, and were, therefore, diagnosed with the syndrome. Participants with metabolic syndrome were on average 6.95 years older than were participants without the syndrome (95% CI: 6.56–7.33, $p < 0.001$). The prevalence of metabolic syndrome was higher in men than in women (18.5% vs. 8.1%, $p < 0.001$). In an unadjusted analysis, participants with metabolic syndrome were found to be at an increased risk of developing cancer (HR 1.58, CI: 1.38–1.8, $p < 0.001$); however, after adjustment for age and sex, no increased risk was found (HR 1.07, CI: 0.94–1.23, $p = 0.3$) (Fig. 3). We also assessed the association between metabolic syndrome and specific cancer types. After adjustment for age, only breast cancer in women was associated with metabolic syndrome (HR 1.67, CI: 1.05–2.67, $p = 0.03$).

3.3. Obesity and cancer incidence

An additional analysis was performed to evaluate the relationship between obesity and overweight and cancer incidence. One thousand three hundred and sixty-eight subjects had missing data on BMI, and were excluded (Fig. 1). The excluded patients did not differ statistically from the general cohort in terms of age, gender, or levels of metabolic components for which data were available. The remainder 23,619 participants were aged 25–97 years (average age 48, SD 10.9); of these, 17,047 (72.2%) were men and 6571 (27.8%) were women. Based on a definition of obesity of BMI greater than 30 kg/m^2, 2900 participants (14.2%) were obese. Participants with obesity were older than non-obese participants (obese 50.1 years (SD 11), non-obese 47.7 years (SD 9.8), $p < 0.001$). The prevalence of obesity was higher in men than in women (65.9% vs. 34.9%, $p < 0.001$). In an unadjusted analysis, participants with BMI greater than 30 kg/m^2 were found to be at an increased

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