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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

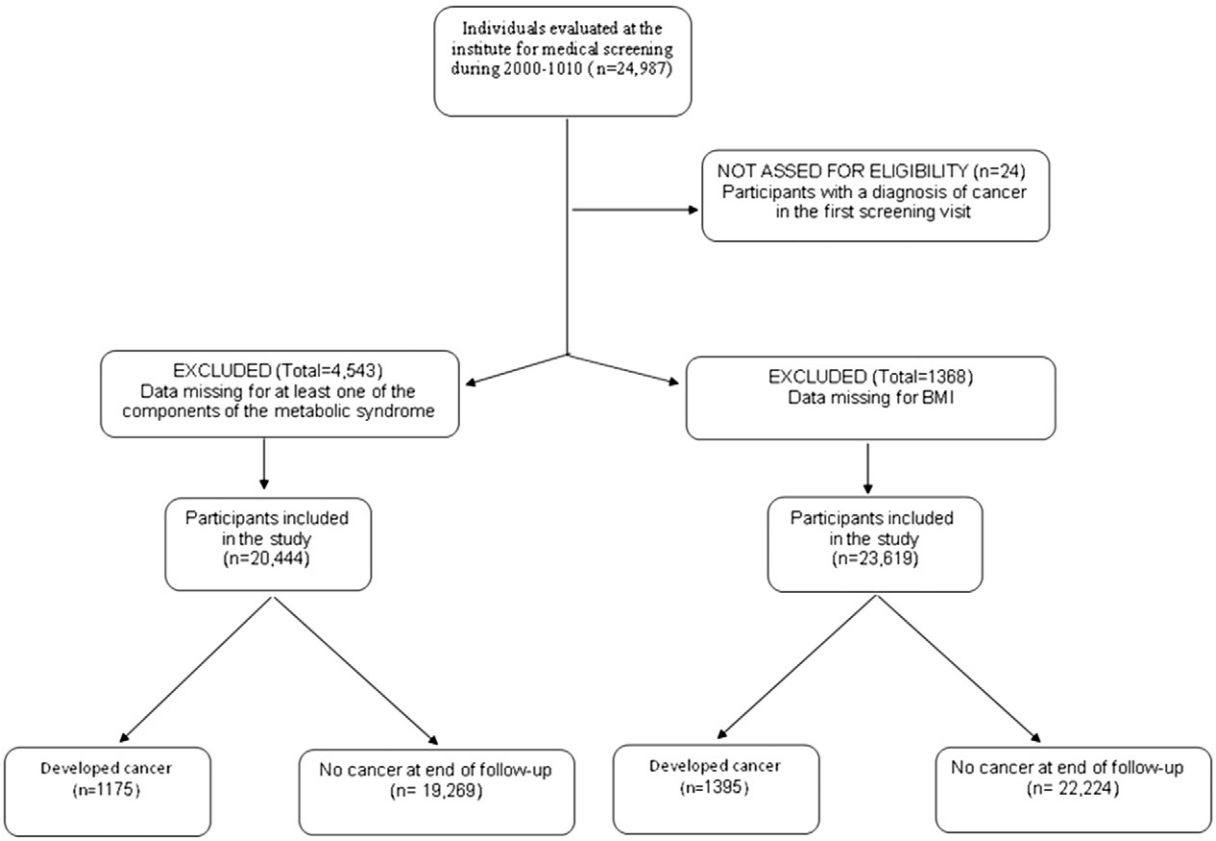

Fig. 1. Flow chart for patient inclusion in the retrospective analysis.

risk of developing cancer (HR 1.15, CI: 1.00–1.33, $p = 0.04$). As was observed in our analysis of the association between metabolic syndrome and cancer, after adjustment for age and sex no increased risk was found (HR 1.09, CI: 0.95–1.26, p = 0.21). Similarly in an unadjusted analysis of the 13,523 participants (57.3%) who were overweight (defined as having a BMI of >25 kg/m^2), we found that a BMI greater than 25 kg/m^2 was correlated with an increased risk of developing cancer (HR 1.22, CI: 1.09–1.36, $p < 0.001$), but after adjustment for age and sex no significant increase risk was found (HR 1.75, CI: 0.96–1.20, $p = 0.12$). We also assessed the association between overweight and

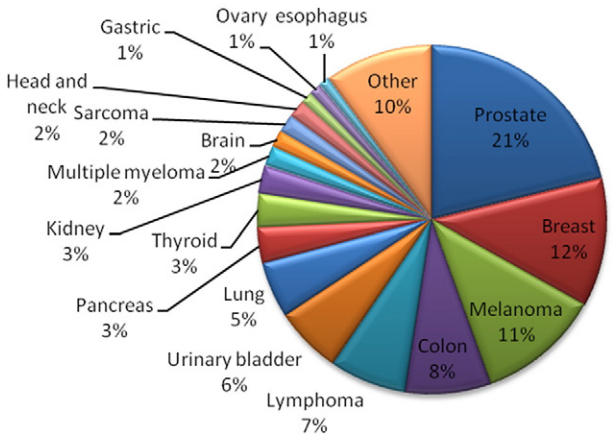

Fig. 2. Specific malignancies diagnosed during follow-up among 20,444 men and women. The percentages of new diagnosed malignancies among 20,444 men and women during mean follow-up of 104.3 months.

Table 1
Cancer types according to gender.

	Cancer prevalence			
Cancer type	Females	Females with cancer	Men	Men with cancer
CNS cancer	0.06%	1%	0.1%	1.7%
Breast cancer	2.7%	46.5%	0.02%	0.3%
Cervical cancer	0.2%	3.9%	0	0
Cholangiocarcinoma	0	0	0.04%	0.7
Colorectal cancer	0.4%	6.2%	0.6%	8.5%
Endometrial cancer	0.2%	2.9%	0	0
Esophageal cancer	0.02%	0.3%	0.1%	1.2%
Gastric cancer	0.03%	0.5%	0.1%	1.3%
Germ cell tumors	0	0	0.1%	1.2%
Hepatoma	0	0	0.01%	0.2%
Head & neck cancer	0.05%	0.8%	0.1%	2.1%
Lymphoma	0.3%	4.4%	0.5%	8%
Melanoma	0.4%	7%	0.9%	12.9%
Meningioma	0.04%	0.8%	0.04%	0.6%
Merkel cell cancer	0	0	0.01%	0.3%
Mesothelioma	0	0	0.01%	0.2%
Myeloma	0.1%	1%	0.1%	2.1%
Neuroendocrine tumor	0.1%	1%	0.1%	1.6%
NSCLC	0.3%	5.2%	0.3%	5%
Ovarian cancer	0.2%	4.4%	0	0
Pancreatic cancer	0.1%	1%	0.3%	3.7%
Prostate cancer	0	0	1.9%	28.3%
Renal cell cancer	0.1%	1.3%	0.2%	3%
Sarcoma	0.03%	0.5%	0.1%	2.1%
SCLC	0	0	0.01%	0.2%
TCC	0.1%	1.8%	0.5%	7.8%
Thyroid cancer	0.3%	5.6%	0.2%	2.3%
Unknown primary	0.1%	1.6%	0.1%	1%
NOS	0.1%	2.3%	0.2%	3.7%

Prevalence of newly diagnosed cancers among 14,913 men and 5531 women in the study cohort. Among whole population and among cancers. NSCLC—non-small cell lung cancer, SCLC—small cell lung cancer, TCC—transitional cell cancer, NOS—not otherwise specified.

Table 2
Prevalence of components of metabolic syndrome in the study population.

Component	Average (SD)	Diagnosis criterion	Number with inclusion criterion (%)
Triglyceride (mg/dL)	129.02 (75.33)	>150 mg/dL	5683 (27.8)
HDL-C (mg/dL)	47.37 (12.25)	<40 mg/dL (men) <50 mg/dL (women)	7905 (38.7)
Fasting glucose (mg/dL)	91.58 (19.89)	>100 mg/dL	3354 (16.4)
Diastolic BP (mm Hg)	78.2 (11.09)	>85 mm Hg	3790 (18.5)
Systolic BP (mm Hg)	123.7 (18.3)	>130 mm Hg	4898 (24)
BMI (kg/m^2)	26.04 (3.98)	>30 kg/m^2	2900 (14.2)

Averages of various components of metabolic syndrome at first visit, criteria for diagnosis of metabolic syndrome, and numbers and percentages of the cohort with a value indicative of metabolic syndrome.

specific cancer types. No association was found between overweight and specific cancers in both genders (data not shown).

4. Discussion

The current study looked at the relationship between metabolic syndrome and weight and incidence of cancer (overall and specific types) in a cohort of asymptomatic patients in Israel who were examined yearly. We demonstrated a significant correlation between the metabolic syndrome and breast cancer in women. However, neither the metabolic syndrome nor BMI over 25 kg/m^2 (overweight) was associated with an increased risk of overall cancer or other cancer types. This is in contrast to several studies in other populations, which did show such an association [6–8]. For an example, data from 5.24 million individuals in the Clinical Practice Research Datalink study demonstrated that high BMI was associated with 17 out of 22 types of cancers [14]. These studies were conducted in the United States, where the prevalence of obesity and metabolic syndrome is much higher than in the population we studied. The prevalence of the metabolic syndrome in the US cohorts was 24%, whereas among subjects in our cohort, it was 15.7%. In the US cohorts, 30% were obese, but only 14.2% of our subjects had BMIs indicative of obesity.

Several studies have suggested that other components of the metabolic syndrome such as impaired fasting glucose and type 2 diabetes mellitus are associated with an increased risk of developing a variety of cancers [15,16], and have a negative effect on cancer survival [17].

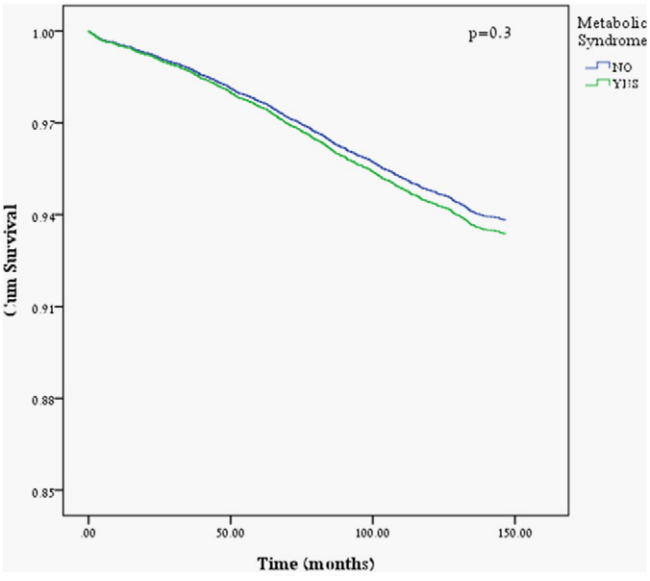

Fig. 3. Cancer-free survival of subjects with and without metabolic syndrome. Kaplan–Meier curve of cancer-free survival as a function of time in patients with metabolic syndrome (green line) and without metabolic syndrome (blue line) adjusted for age and sex.

In addition a higher incidence of cancer was demonstrated in patients with hypercholesterolemia [18–20], and hypertriglyceridemia (especially prostate cancer) [21,22]. Regarding high blood pressure results are rather controversial; several studies found an independent cancer risk [23,24], while others did not [25,26].

The incidence of cancer in our cohort (5.7%) was higher than the incidence of cancer in Israel [27]. The population we studied is different from the general Israeli population in several ways. Most of the participants in The Institute for Medical Screening at the Chaim Sheba Medical Center are Jewish of Ashkenazi origin, whereas about 20% of Israeli citizens are non-Jewish (mostly Muslim Arabs) and 40% are non-Ashkenazi Jewish. Cancer incidence in Israeli Jews is higher than in non-Jews (3.7% vs. 1.2%) [27], and is higher in Ashkenazi than in Sephardi Jews [28–30]. Moreover, the participants are older: the median age was 48 vs. 29.5 in the general Israeli population [31]. The medical examination at the Institute for Medical Screening includes several cancer screening examinations (a thorough physical examination including dermatological, breast and gynecological examination, occult fecal blood, PSA, and mammography). The incidence of cancers potentially diagnosed by these measures in our cohort was lower than in the general Israeli population [32].

Several possible mechanisms of an association between the metabolic syndrome, obesity and cancer have been proposed. Insulin resistance and hyperglycemia are common in patients with metabolic syndrome and obesity and are associated with abnormally high levels of insulin-like growth factor-1 and leptin and abnormally low levels of adiponectin. These metabolic abnormalities may act as growth factors increasing the risk for cancer. Increased levels of plasminogen activator inhibitor 1 and vascular endothelial growth factor, observed in patients with metabolic syndrome and obesity, may increase angiogenesis and tumor progression. Chronic inflammation, which is also common in subjects with these conditions, is also known to be associated with an increased risk of cancer [33–36].

The only significant association we found in our study was between metabolic syndrome and breast cancer in women. In previous studies, metabolic syndrome was found to be associated with a decreased risk of breast cancer in pre-menopausal women and an increased risk in post-menopausal ones [7,37]. In a meta-analysis of Esposito K and collages, which included 6417 post-menopausal women metabolic syndrome was associated with a moderately increased risk for breast cancer. No single component of the metabolic syndrome explained the elevated risk [16]. Another case control study involving Swiss and Italian post-menopausal women demonstrated that participants diagnosed with breast cancer had an increased rate of metabolic syndrome compared to those without cancer [15]. We did not have information about the menopausal status of women in our study, but their average age of 46.8 is consistent most being post-menopausal. Several mechanisms were proposed to explain the association between the metabolic syndrome and post-menopausal breast cancer. Increased conversion of androgens to estrogen in adipocytes and decreased levels of sex hormone binding globulin in post-menopausal relative to pre-menopausal women may increase blood levels of free estrogen after menopause, an established risk factor for breast cancer [38].

Several limitations of our study should be mentioned. First, the study population tends to represent a higher than average socioeconomic population in Israel with high percentage of Ashkenazi Jews. In addition socioeconomic status is associated with both an increased incidence of the metabolic syndrome [39] and cancer [40]. Second, we did not have data concerning waist circumference and had to substitute with BMI. Waist circumference was chosen as a criterion for the metabolic syndrome, since it is better correlated with the metabolic derangements typical of that syndrome [11]. Therefore, the assignment of the diagnosis of the metabolic syndrome (or lack of thereof) may have not been accurate in some participants.

In summary, in a population of mostly Jewish males with a higher than average socioeconomic status, no association was found between metabolic syndrome or weight and the risk of cancer. The only significant association found was between metabolic syndrome and breast cancer in women.

Conflict of interests

This study was funded entirely by the authors and they have no conflict of interest with any third party.

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