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Baseline metabolic disturbances and the twenty-five years risk of incident cancer in a Mediterranean population

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Abstract *Background and aims:* Obesity is predictive of metabolic syndrome (metS), type 2 diabetes, cardiovascular (CV) disease and cancer. The aim of the study is to assess the risk of incident cancer connected to obesity and metS in a Mediterranean population characterized by a high prevalence of obesity.

Methods and results: As many as 1133 subjects were enrolled in two phases and followed for 25 years (859 subjects) or 11 years (274 subjects) and incident cancer was registered in the follow-up period. Anthropometric measures and biochemical parameters were filed at baseline and evaluated as predictors of incident cancer by measuring hazards ratios (HR) using multivariate Cox parametric hazards models. Best predictive threshold for metabolic parameters and metS criteria were recalculated by ROC analysis.

Fasting Blood Glucose >5.19 mmol/L [HR = 1.58 (1.0–2.4)] and the TG/HDL ratio ($\log_{10}$) (Males > 0.225, Females > 0.272) [HR = 2.44 (1.3–4.4)] resulted independent predictors of survival free of cancer with a clear additive effect together with age classes [45–65 years, HR = 2.47 (1.3–4.4), 65–75 years HR = 3.80 (2.0–7.1)] and male gender [HR = 2.07 (2.3–3.1)].

Conclusions: Metabolic disturbances are predictive of cancer in a 25 years follow-up of a Mediterranean population following a traditional Mediterranean diet. The high prevalence of obesity and metS and the observed underlying condition of insulin resistance expose this population to an increased risk of cardiovascular disease and cancer despite the healthy nutritional habits.
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Introduction

Obesity is considered the global epidemic of the 21st century by the World Health Organization (WHO) [1]. About 50 years ago, epidemiological studies [2] have indicated that the healthy dietary habits of Mediterranean populations were associated with cardiovascular (CV) protection, and the adherence to the "Mediterranean diet", codified in those epidemiological studies, proved to be the first line of action in reducing populations' cardiovascular risk [3]. Nevertheless, modification of the traditional lifestyle in Mediterranean countries have led to a substantial increase in obesity and its related consequences, as metabolic syndrome (metS), type 2 diabetes and CV disease [4].

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Obesity and metabolic disturbances are related also to the risk of cancer [5–7], which represents one of the principal causes of mortality also in the Mediterranean area [8]. A large meta-analysis from the World Cancer Research Fund/American Institute for Cancer Research has confirmed the association between obesity, type 2 diabetes and several types of cancers [9]. Two adipokines, adiponectin (adpn) and leptin (lep), and their relative receptors have been associated to cancer development [10]. Several single nucleotide polymorphisms (SNPs) in the *ADIPOQ* (encoding for adpn), *ADIPOR1*, *ADIPOR2* (encoding for adpn receptors) genes have been associated to obesity [11], insulin sensitivity [12], MetS [13] inflammation and cancer [14,15]. Also SNPs in the *LEP* gene (encoding for lep) and in the *LEPR* gene (encoding or the lep receptor) have been associated to breast and other types of cancers [16].

The Ventimiglia Heart Study is an epidemiological project started in 1989 with the aim to survey a whole population of a small Sicilian rural community located in the countryside and characterized by nutritional habits [17] that resembled the Mediterranean diet at the beginning of the study, but with a high prevalence of obesity in the population within the 40–60 years range of age [17]. Population's health has been monitored since then, and the project is still ongoing.

The aim of the present study was to evaluate if the anthropometric and metabolic parameters measured at baseline resulted predictive of cancer in the 25 years follow-up.

Methods

Study population

The characteristics of the Ventimiglia Heart Study have been described in details elsewhere [18]. Briefly, the population was enrolled in the study in the 1989, with an attendance rate of 75%. At the end of the first enrollment phase 1351 subjects (622 males, 729 females) were enrolled.

A clinical record including family and personal clinical history and lifestyle habits was filed. A medical examination with anthropometric measurements and EKG were conducted by a team of physicians, while a blood sample was drawn in order to assay several biochemical and hematological variables. Obesity and overweight were defined according to WHO definitions [1], while MetS was diagnosed according to the consensus definition of MetS issued by International Diabetes Federation, National Heart Lung and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity [19], and the adopted criteria will be defined in this paper as "consensus" criteria from now on. Visceral adiposity index (VAI), a surrogate measure of visceral fat function, was calculated as described elsewhere [20].

For the present study, only 859 subjects in the 25–75 years range of age were selected from first enrollment. Follow-up time was 25 years for these subjects. A second enrollment phase was conducted in 2003, and 617 subjects in the same range of age were enrolled. A blood bank was established only during the second enrollment. Since some of the subjects overlapped with those from the first enrollment phase, only 274 new subjects were filed in the study after the second phase, with a follow-up time of 13 years. A total of 1133 subjects (859 from phase one, 274 from phase 2) resulted included in the present study. The time-line and the schema of the present study are explained in the Supplementary Fig. 1.

The adopted procedures were in accordance with the Helsinki Declaration of 1975, as revised in 1983 and were approved by the Ethical Committee of the University of Palermo. All the subjects gave their informed consent to both genetic testing and procedures out of clinical routine prior to participate to the study.

Analysis of events

We registered new cases of cancer and mortality over a period of 25 years. Follow-up time was 25 years (1989–2014) in the 859 subjects from the first enrollment and 11 years (2003–2014) in the 274 subjects from the second enrollment.

Primary end-point was the incidence of any type of cancer. Secondary end-point was total mortality. All events were collected with the help of a team of physicians that included General Practitioners and Specialists in Internal Medicine, Geriatrics, Cardiology and Pathology that was in charge of revising the filed events. Cancer data originated from review of General Practitioners clinical data, from hospital discharge documentations or from death certifications in the case of a fatal event of any kind.

Laboratory procedures

Routine analyses were performed according to standard procedures as described elsewhere [17,18]. Laboratory determinations at baseline were measured separately in the first and second enrollment phase of the study. The data were checked for homogeneity before merging the two subsets of data. Biochemical data were pooled only if the means of the two laboratory determinations were not significantly different by the Student t-test of unpaired data.

Statistics

Differences in biochemical and clinical parameters between subjects with and without incident cancer were evaluated by ANOVA test after adjustment for age and gender as covariates. Parameters were checked for normal distribution by the Kolmogorov–Smirnov test. Whenever normal distribution was not confirmed, logarithmic transformation of the data was applied. Differences of prevalence rates for dichotomous variables were assessed by $\chi 2$ test with the Mantel–Haenszel adjustment for age and gender classes. Yates correction was also applied.

Best thresholds predictive of incident cancer (in terms of best sensitivity and specificity) were evaluated by ROC

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