

Modified metabolic syndrome and second cancers in women: A case control study

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Abstract

Background: According to some studies, the metabolic syndrome causes diverse primary cancers; however, there is no evidence about metabolic syndrome impact on second cancers development in women. **Aim:** To find out the implication of the modified metabolic syndrome in women with second cancers. **Materials and Methods:** This was a case-control study, at a general hospital in Mexico City, in women with second cancers (cases) and age-matched women with only one neoplasm (controls). The analysis comprised: Tumor (s), anthropometric features, and body mass index (BMI); moreover, presence of diabetes mellitus, hypertension, and fasting serum levels of total cholesterol, triglycerides and glucose. **Results:** The sample was of nine cases and 27 controls. In cases, the metabolic syndrome (diabetes mellitus or glucose > 99 mg/dL + hypertension or blood pressure \geq 135/85 mm Hg + triglycerides > 149 mg/dL or BMI \geq 30 kg/m²) was more frequent (odds ratio 20.8, 95% confidence interval: 1.9–227.1). **Conclusion:** Our results suggest that in women, the modified metabolic syndrome may be a risk factor for second cancers.

Key words: Adult; cancer, female, metabolic syndrome, Mexico, neoplasms, neoplasms, second primary/etiology, obesity

Introduction

Worldwide the number of cancer survivors is raising;^[1,2] for example, in the U.S. cancer survivors increased from 3 million in 1971 to over 12 million in 2011.^[2] These survivors are at risk to develop life-threatening second malignancies.^[3-5] Among the multiple sources behind the appearance of these new cancers are obesity, hypertension, and diabetes mellitus.^[5-10] Furthermore, those three diseases makeup elements of a pathologic condition common in cancer survivors: The metabolic syndrome.^[11]

Metabolic syndrome is a cluster of disorders characterized by insulin resistance, hypertension, dyslipidemia, functional endothelial dysfunction, and obesity.^[11] Some researchers have indicated that the metabolic syndrome causes certain malignancies.^[12] Therefore, if this syndrome promotes several primary cancers, there are huge possibilities that in cancer survivors, it may cause second malignancies. However, to our knowledge, there are not studies approaching this issue.

The aim of this case-control study was to find out the plausible implication of the metabolic syndrome in women with second cancers.

Materials and Methods

Patients

Female cancer survivors (survival \geq 2 years after completing oncologic treatment) with two or more different cancers were chosen as cases. And for each case three, randomly selected, age-matched female survivors with a neoplasm similar to the first neoplasm of cases, but without a second malignancy, were chosen.

Data collection and definitions

From medical files, recent data concerning: Age, blood pressure, weight and height, as well as, their malignant tumor(s), oncologic treatments, associated diseases (diabetes mellitus, hypertension, and dyslipidemia); medications used and fasting serum levels of glucose, triglycerides, and total cholesterol were obtained.

Recent data were registered from the last semester of clinical follow-up. Blood pressure was measured with a sphygmomanometer in the supine position after a 10-min rest. Weight was determined barefooted and in underwear on a mechanic scale, and recorded to the nearest 0.1 kg, and height was measured with a stadiometer to the closest 0.5 cm. Body mass index (BMI) was calculated: Weight in kilograms divided by the square of height in meters (kg/m²).

Second malignancies were diagnosed when a woman developed distinct cancers (histologically different), in different organs, more than 6 months after diagnosis of the first neoplasia. Diabetes mellitus was diagnosed if the subject used insulin or oral hypoglycemic agents or by fasting serum glucose \geq 126 mg/dL. Hypertension was diagnosed by use of antihypertensive or blood pressure values \geq 135/85 mm Hg. Dyslipidemia was diagnosed by use of fibrates, statins or total cholesterol > 199 mg/dL or triglycerides > 149 mg/dL. The modified metabolic syndrome was diagnosed when three of the following parameters appeared simultaneously: Obesity (BMI \geq 30 kg/m²), previous diagnosis of diabetes mellitus or fasting serum glucose levels > 99 mg/dL, previous diagnosis of hypertriglyceridemia or triglycerides > 149 mg/dL, or previous diagnosis of hypertension or blood pressure \geq 135/85 mm Hg.

Statistical analysis

The sample size was calculated using the formula: $n = [EDFF \times Np(1-p)] / [(d2/Z21 - \alpha/2 \times (N-1) + P \times (1-p)]$, with a 0.05 alpha and a 0.8 beta, with 6% of controls and 54% of cases exposed. All values were expressed either in absolute numbers or percentages. Data were analyzed with the Pearson's " χ^2 " or exact Fischer's test; the latter when any value was \leq 5 in any cell of the 2×2 table. Association strength between variables was studied with odds ratio, with a 95% confidence interval. For all analyses, the statistic program OpenEpi version 2 (www.openepi.com) was used, all value of $P < 0.05$ were considered statistically significant.

Results

The calculated sample was of 7 cases and 19 controls; however, we increased it to 9 cases and 27 controls. In the cases, the most frequent primary or secondary tumor was breast cancer (11/19, 58%), [Table 1].

Cases were on average heavier than controls; nevertheless, both groups had similar mean high-levels of glucose, cholesterol, and triglycerides [Table 2].

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Finally, the data analysis revealed that the modified metabolic syndrome was the most significant risk factor [Table 3].

Discussion

In this case-control study, at a second-level general hospital, the modified metabolic syndrome was the most significant risk factor in Mexican women with second cancers. This is relevant because world-wide the metabolic syndrome is extremely frequent due to obesity's pandemia.^[6] Particularly, Mexico is facing the greatest incidence of obesity^[13] and so, diseases associated to it have increased, including cancer and the metabolic syndrome.^[14] However, there are no studies regarding the influence of the metabolic syndrome on women's second cancers.

There is, however, ample evidence supporting that the metabolic syndrome is a risk factor for many primary malignancies. It increases the risk for: Breast,^[15-20] endometrial,^[21-23] cervical,^[24] and colorectal cancers.^[12]

Moreover, there are studies documenting that even some of metabolic syndrome's single components increase the risk for some second cancers. Such is the case for obesity (in breast, renal and colorectal cancers),^[7,10,25] insulin resistance (in breast, renal and colorectal cancers),^[25-28] hypertension (in breast and renal cancers),^[25,29] and hypertriglyceridemia (in renal and cervical cancers).^[25,30] There is also evidence that when these components are associated, but without integrating the syndrome, they considerably increase the risk for some second cancers.^[21,29,31]

The different impact of individual components and of the full syndrome has also been observed in nononcological areas. Glance *et al.*, for example, showed that individuals with the

modified metabolic syndrome are at a significant greater risk of surgical complications than obese subjects without the syndrome.^[32]

The predominance of second breast cancers we found [Table 1] is consistent with different reports of Africa,^[33] America,^[10,34] Asia,^[35] and Europe.^[3] This is particularly relevant, considering that world-wide breast cancer is one of the main tumors. For example, breast cancer survivors are the most numerous in the U.S.^[2]

The mechanisms involved in the induction of cancer by metabolic syndrome may be multiple, acts synergistically, and are yet poorly understood. The most studied are: Hyperinsulinemia, secondary to insulin resistance, high-levels of glucose and insulin-like growth factor, reduced levels of sex hormone binding-globulin with high free estrogen levels, and high-levels of leptin and fatty acids.^[11,25-30]

Often, second malignancies are lethal in cancer survivors because they are detected in advanced stages,^[3,33,36] perhaps, due to low use of screening studies.^[37] If other researchers corroborate our findings, probably, there is a major need to establish cancer screening studies in survivors with modified metabolic syndrome. In addition, future studies should address whether or not metabolic syndrome's treatment may decrease the incidence of second malignancies in cancer survivors; particularly, that of its key etiological component: The obesity.

We are quite aware of the limitations of this study, which include a rather small sample size a population of a single hospital, a heterogeneous group of cancers, and the lack of waist circumference data. Our findings are, nonetheless, in line with those reported by most other studies of the relationship between the metabolic syndrome and cancer.

Conclusion

We suggest that the modified metabolic syndrome in women survivors of cancer may be a risk factor for second neoplasms. If others corroborate our findings, there is a greater need to launch screening studies in cancer survivors with the metabolic syndrome.

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Table 1: Cases and their neoplasms

Case	Age (years)	1 st neoplasm	2 nd neoplasm	3 rd neoplasm
1	60	Endometrial	Renal	-
2	67	Breast	Rectum	-
3	71	Breast	Breast	-
4	67	Breast	Renal	Cervical
5	62	Cervical	Breast	-
6	56	Breast	Breast	-
7	78	Breast	Cervical	-
8	73	Endometrial	Breast	-
9	43	Breast	Breast	-

Table 2: Quantitative variables

Variables	Media (SD)	
	Cases n=9	Controls n=27
BMI (kg/m ²)	34 (7)	27 (5)
Glucose (mg/dL)	118 (37)	109 (23)
Cholesterol (mg/dL)	246 (39)	243 (46)
Triglycerides (mg/dL)	199 (113)	208 (131)

BMI=Body mass index, SD=Standard deviation

Table 3: Analysis of qualitative variables

Variables	n (%)		P	OR (95% CI)
	Cases n=9	Controls n=27		
Modified metabolic syndrome	4 (44)	1 (4)	0.01	20.8 (1.9-227.1)
DM+hypertension	4 (44)	2 (7)	0.04	10 (1.42-70.29)
BMI ≥30 kg/m ²	6 (67)	7 (26)	0.07	5.7 (1.11-29.2)
BMI <30 kg/m ²	3 (33)	20 (74)	0.07	0.17 (0.03-0.89)

BMI=Body mass index, CI=Confidence interval, DM=Diabetes mellitus, OR=Odds ratio

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