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Differences in Dietary Components and Oxidative Stress Markers between Cervical Cancer Patients and Matched Controls

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Abstract

Background and objective: Cervical cancer is a leading cause of death among women in developing countries. Diet has been suggested to play an important role in the pathophysiology of malignant tumors as an imbalance between dietary antioxidant intake and free radical production-from the inflammatory state- results in oxidative stress, which may contibute to both initiation and progression of carcinogenesis. The aims of the present study were to assess the difference regarding dietary intake and oxidative stress plasmatic markers differences between cervical cancer patients and matched controls.

Methods: A case-control study -nested within a larger clinical trial- including 100 patients diagnosed with locally advanced cervical cancer and 80 women without the malignant disease was conducted. A food frequency questionnaire was used for assessing diet. Plasmatic oxidative stress markers -malondialdehyde and free carbonyls- were also determined.

Results: Patients with cervical cancer presented a significantly higher body mass index and higher consumption of dietary protein and fat, niacin, cholesterol, sodium, cyanocobalamin, vitamin E, and zinc. A significantly lower intake of vitamin C was found in the case group. MDA levels were found to be statistically higher in cervical cancer patients while free carbonyls did not show significant differences.

Conclusions: A high-fat/high-protein diet, together with lower consuption of ascorbic acid may contribute to an increase risk of developing cervical cancer. However, further prospective and longitudinal research should be promoted in order to elucidate such associations.

Keywords

Antioxidants, Case-control study, Cervical cancer, Diet, Oxidative stress

Introduction

According to the World Health Organization (WHO), cancer is a leading cause of mortality worldwide, accounting for approximately 13% of all deaths [1]. Among women, cervical cancer is the third most common malignancy; its incidence and mortality is significantly higher in developing countries [2].

Infection from Human Papilloma Virus (HPV) is recognized as the most common cause of such gynecologic cancer [3]; however, certain components within lifestyle –e.g., tobacco smoking, excessive alcohol drinking, use of oral contraceptives, and obesity- are also considered as risk factors [4]. Obesity has been implicated in the pathophysiology of several neoplasms, such as breast, colon, prostate, stomach, and cervical cancers. For its side, dietary components with the strongest association to these diseases include excessive energy (caloric) intake, fat, cholesterol, and alcohol, together with an insufficient consumption of fiber, calcium, vitamins A, E and C, folic acid, and selenium [5].

All of the above participate in the redox balance. Whenever such equilibrium is disrupted, oxidative stress develops as a result of either excess free radical production or insufficient antioxidant mechanisms (both endogenous and exogenous) [6]. In turn, this aberrant state has been suggested to be closely linked to cancer, as the latter implies chronic inflammation that may contribute to the transformation of normal cells to tumor cells [7].

Due to all the mentioned variables, we conducted a study aimed to assess whether diet and oxidative stress markers differed between cervical cancer patients and women without the malignancy, and thus could be considered as potential risk factors.

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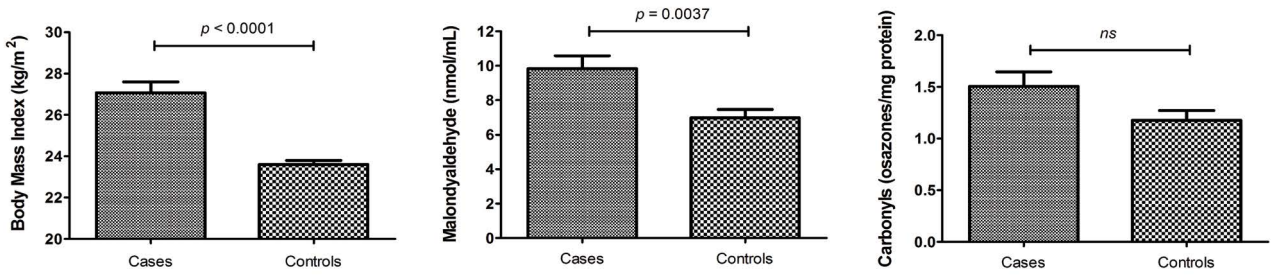

Figure 1: Comparison of body mass index, plasma malondialdehyde and carbonyls (as markers of oxidative stress) in cervical cancer patients (cases) and matching controls. *p*-values are shown after performing Student's t-test for independent samples.

Table 1: Data analysis from food frequency questionnaire

Dietary component	Cases (n=100)	Controls (n=80)	*p*-value
Total energy (kcal/day)	2454 ± 85.27	2650 ± 103.1	*Ns*
Protein kcal from total energy value (%)	25.89 ± 3.626	14.60 ± 0.3470	0.0077
Fat kcal from total energy value (%)	56.39 ± 8.177	22.78 ± 0.6346	0.0005
Carbohydrate kcal from total energy value (%)	39.40 ± 3.855	65.81 ± 1.040	<0.0001
Niacin	48.01 ± 3.338	24.68 ± 1.091	<0.0001
Iron	20.43 ± 1.008	20.46 ± 0.9074	*Ns*
Thiamin	3.448 ± 0.9198	2.289 ± 0.1036	*Ns*
Riboflavin	3.694 ± 0.9157	2.585 ± 0.1240	*Ns*
Calcium	754.6 ± 30.90	1014 ± 49.03	<0.0001
Ascorbic acid	168.7 ± 9.105	268.1 ± 24.29	<0.0001
Retinol	3114 ± 262.5	2628 ± 304.8	*Ns*
Cholesterol (mg)	622.3 ± 44.22	342.5 ± 20.13	<0.0001
Sodium (mg)	3297 ± 217.6	1978 ± 94.04	<0.0001
Fiber (g)	12.57 ± 0.9623	14.79 ± 0.8381	*Ns*
Vitamin B_6	4.183 ± 0.9200	2.148 ± 0.1314	*Ns*
Vitamin B_{12}	33.91 ± 3.364	6.407 ± 0.5807	<0.0001
Folate	247.2 ± 13.62	223.0 ± 14.04	*Ns*
Pantothenic acid	4.735±0.9075	5.369 ± 0.2887	*Ns*
Vitamin E	12.71 ± 1.220	3.400 ± 0.3228	<0.0001
Saturated fat (g)	37.70 ± 2.012	23.29 ± 1.481	<0.0001
Monounsaturated fat (g)	36.02 ± 1.754	22.16 ± 1.246	<0.0001
Polyunsaturated fat (g)	40.97 ± 2.428	13.16 ± 0.8369	<0.0001
Cupper	1.924 ± 0.9261	1.168 ± 0.07171	*Ns*
Magnesium	321.2 ± 13.34	330.6 ± 19.17	*Ns*
Phosphorous	914.9 ± 32.85	1051 ± 54.88	0.0269
Potassium	3512 ± 137.3	3812 ± 232.4	*Ns*
Selenium	11.23 ± 1.107	10.46 ± 1.698	*Ns*
Zinc	12.25 ± 1.014	9.252 ± 0.9799	0.0393
Water (mL)	823.2 ± 38.37	2174 ± 113.4	<0.0001

Methods

A case-control study -nested to a larger clinical trial- including patients diagnosed with locally advanced cervical cancer and matched (for age, socioeconomic status, education, etc.) controls without the malignant disease was conducted at Hospital General de México, O.D. from February to December, 2008. Exclusion criteria were obesity (body mass index ≥ 30kg/m^2), diabetes, and hypertension.

Prior to any antineoplastic treatment, diet was assessed with a food frequency questionnaire, validated for Mexican population [8]. Further, a 5mL blood sample was taken in order to determine plasmatic malondialdehyde (MDA) and free carbonyls as oxidative stress markers through colorimetric methods (as reported in the literature) [9-11].

The protocol was approved by the Institutional (Hospital General de México. O.D.) Ethics and Research committees. All participants signed a written informed consent before any procedure. The study was conducted in agreement with local law regulation [12], Helsinki Declaration [13], and Good Clinical Practice guidelines [14].

Results are presented as mean ± standard error, unless otherwise stated. Student's independent t-tests were performed and a statistical significance was considered when *p*-value was <0.05.

Results

The study included 100 cases with diagnosed locally advanced cervical cancer and 80 matched controls without the malignant disease. As described in figure 1, patients with malignant disease showed a significantly higher body mass index (BMI) (27.07 ± 0.52 vs. 23.60 ± 0.19kg/m^2) and MDA levels (9.82 ± 0.75 vs. 6.98 ± 0.48). Plasmatic carbonyls were not different between cases and controls; however, a lower value was found in volunteers without cancer (1.50 ± 0.14 vs. 1.17 ± 0.09).

Table 1 shows the data obtained from the analysis of food frequency questionnaire. Even though total daily energy intake was not different between groups, macronutrient distribution had statistically significant differences: while control's diet was balanced-according to national recommendations-, patients with cervical cancer were found to consume a high-protein and high-fat diet, concomitant to a lower intake of carbohydrates.

Significantly higher intake of niacin, cholesterol, sodium, cyanocobalamin, vitamin E, fats (saturated, monounsaturated, and polyunsaturated), and zinc in the case group was found. In addition, significantly lower amounts of calcium, vitamin C, phosphorous, and water were consumed by cancer patients.

Discussion

Like other malignant diseases, cervical cancer have been proven to enhance oxidative stress both by decreasing antioxidant defense molecules (e.g., glutathione) [15], and by generating reactive oxygen species [16]. In the present study, this fact was confirmed as plasma MDA was significantly higher in the case group; such phenomenon has also been described by other authors [17-19], who suggest that oxidative stress may play an important role in the pathogenesis of cervical malignant disease. However, because of study designs – including the present- it has not been possible to conclude such statement, as these investigations are retrospective hence susceptible to bias.

A novel aspect of the study was the evaluation of nutrition status between cases and controls. Cases presented a significantly higher BMI than controls, in fact, the mean value fell within the overweight criteria range. The importance of such finding is that overweight and obesity are two conditions that have also been associated with oxidative stress since they, as cancer does, enhance the secretion of pro-inflammatory molecules which, in turn, increase reactive species [20].

For its side, an inadequate diet has also been proposed as a potential risk factor for all cancers. Although other studies have not found associations between dietary intake (e.g., fruit, milk, or specific nutrients such as vitamin D or folic acid, etc.) [21,22], similar to the findings in this study, meta-analysis have indicated that women with cervical dysplasia usually have significantly lower intakes of dietary antioxidants-considered as preventive factors for the development of neoplasms-including vitamin C, vitamin A, and carotenes [23,24]. Zinc, for its side, serves as cofactor for antioxidant enzymes (i.e., superoxide dismutase); thus other authors have proposed that zinc deficiency may be a risk factor for cervical cancer [25]. However, cancer patients were found to, unexpectedly, report significantly higher intakes of such mineral. Interestingly, there are few investigations on this regard and, in fact, they zinc is positively associated with gynecological cancer [26], although no clear molecular mechanisms explaining a direct causal relationship have been proposed.

Statistically significant lower dietary calcium vs. the control group was also found among the cases. Evidence regarding this mineral and malignant disease has been previously published: a group of researchers found that higher intakes of calcium were negatively associated with the risk of developing colon and rectal cancer [27]. Such phenomenon has also been described for cervical cancer [28]. Again, no conclusive mechanisms have been established but preclinical studies suggest that calcium is able to modulate cell differentiation, proliferation, adhesion, migration and death [29,30], thus higher intakes may exert a protective effect against gynecologic cancerous lesions.

Finally, the control group presented with normal total energy value distribution from macronutrients, while the cases group had a high-fat, high-protein, low-carbohydrate diet, together with mean values of cholesterol and sodium that exceeded the recommended daily allowances (<300mg and <2400mg, respectively). Moreover, this same group consumed significantly higher amounts of saturated fat. Such type of diet corresponds to that of a Western pattern, which has been associated with tumorigenesis in both preclinical and clinical scenarios [31].

An inadequate diet has been associated with an increased risk for all types of cancer, including cervical. Several dietary and nutrition status components may, in turn, increase the already disrupted redox-balance within the organism. However, there is a lack of scientific literature regarding specific relationships between food take and carcinogenesis. The findings presented in this study, clearly indicate that more research should be promoted in order to improving medical nutrition therapy at the primary and secondary levels of prevention for cervical cancer.

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