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Cardiovascular and metabolic pathologies associated with endometrial cancer

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Abstract

Endometrial cancers are one of the most frequent types of gynecological neoplasia in developed countries. In postmenopausal women, the risk of endometrial cancer is about 20%. In premenopausal women below 45 years, the risk is increased when other risk factors for endometrial cancer is associated. It is know that old age, long-term exposure to estrogens, life in developed countries, obesity and metabolic syndrome are the main risk factors for endometrial cancer. The aim of this study is to analyze if there is an association between a series of cardiovascular and metabolic pathologies and endometrial cancer. We perform a retrospective study using all patients admitted in a university hospital, with gynecological pathologies, on a period of two years. From the total number of cases 3030 were excluded 616 patients with other type of neoplasia (either gynecological or non-gynecological). We analyzed the main cardiovascular and metabolic related variables: age, obesity, menopause, diabetes, renal lithiasis, ischemic heart diseases, hypertension, increased cholesterol levels, changes in the reserve lipids, the presence of varicose veins and related hematological and biochemical parameters. Our study showed a significant association between endometrial carcinoma and diabetes (OR=5.1), renal lithiasis (OR=3.60), ischemic heart disease (OR=5.71), changes in reserve lipids (OR=4.1), hypercholesterolemia (OR=3.96), obesity (OR=3.49), arterial hypertension (OR=5.2), and the presence of varicose veins (OR=3.27). This association cannot be explained by increasing age or obesity alone without other risk factors. However, these are not the only cardio-vascular factors that should be looked for in order to decrease the morbidity and mortality in endometrial cancer.
Keywords: *endometrial cancer, metabolic syndrome, obesity, hypertension, risk factors*

Introduction

Endometrial cancers are one of the most frequent types of gynecological neoplasia in developed countries, having a prevalence ranging from 16.3/100,000 women in El Salvator and Canada to 34.1/100,000 women in Barbados[(1)]. The clinical suspicion of endometrial carcinoma is raised by the presence of an abnormal gynecological hemorrhage after taking into account other symptoms, age and the presence of other risk factors[(2)]. In postmenopausal women the risk of endometrial cancer (Figure 1) is about 20% when such a hemorrhage is identified. In women over 45 that are not at menopause, the risk is increased if the period between menstrual cycles is under 21 days, if the volume is significantly increased (over 80 ml) or if the duration is significantly increased (over 7 days)[(3)]. In premenopausal women below 45 years, the risk is increased if there are identifiable abnormal and persistent bleedings, associated with other risk factors for endometrial cancer[(4)]. After Ammant et al, the most important factors increasing the risk for endometrial cancer are: increasing age, long-term exposure to estrogens, residence in North America or Europe, metabolic syndrome, years of menstruation, nulliparity, history of breast cancer, long-term use of Tamoxifen, hormone-replacement therapy with less than 12-14 days of progestagens, or first degree relative

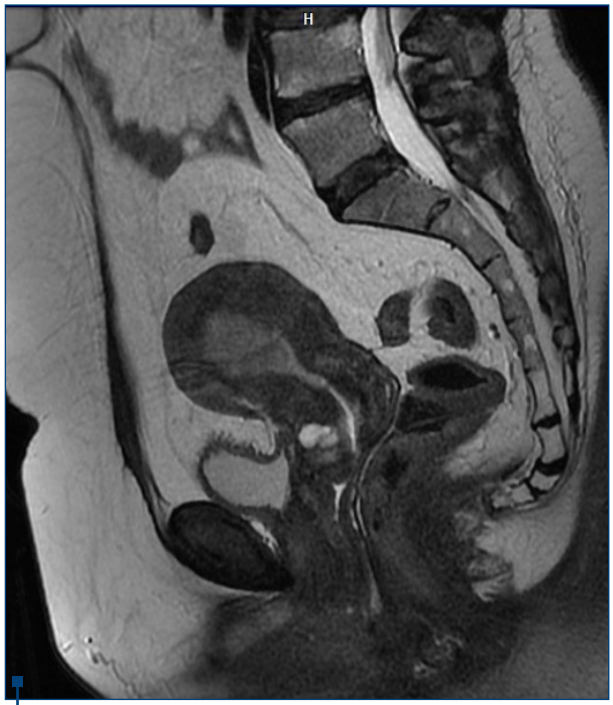

Figure 1. T2b stage endometrial tumor. Sagital T2 FRFSE

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with endometrial cancer[5]. Obesity is known to increase the risk of endometrial cancer[6]. Some authors found an association between various cardiovascular and metabolic diseases like diabetes and hypertension and the risk of endometrial cancer, that seemed to be independent of the presence of obesity[7]. The presence of such diseases is know to be associated with an increased morbidity and mortality in various cancers, as they can decrease the number of therapeutic options, or may need adjustment of the dosage of either radio or chemotherapy[8-11]. The purpose of this article is to analyze if there is an association between a series of cardiovascular and metabolic pathologies and endometrial cancer.

Methods

Retrospective study, using a cohort of patients admitted in a tertiary, university hospital, with gynecological pathologies, on a period of two years. A total number of 3030 patients were initially included, from which 616 patients were excluded due to the presence of other neoplasia (either gynecological or non-gynecological). Of the remaining 2414 patients, 83 had an endometrial carcinoma and 2331 were used as a control group. We included in the database the main cardiovascular and metabolic related variables: age, obesity, menopause, diabetes, renal lithiasis, ischemic heart diseases, hypertension, increased cholesterol levels, changes in the reserve lipids, and the presence of varicose veins. We also analyzed related hematological and biochemical parameters, including cholesterol, triglyceride, uric acid, blood glucose levels, urea, and creatinine. Data was initially included in an Excel database, and then exported in an SPSS (*.sav) database. Statistical analysis was performed using SPSS software, v.20. Descriptive tests, tests for the normality of distribution (Kolmogorov-Smirnof), analysis of variance, analysis of association between qualitative variables (Pearson Chi2, Fisher Exact tests), and binary logistic analysis were used. A p value of 0.05 or lower was considered statistically significant. Due to the frequency of the disease in the general population, Odds Ratio (OR) was considered as similar to the Relative Risk (RR) in binary logistic analysis.

Results

The patients having endometrial carcinoma had a significantly higher age compared to the control group (61.8±8.8 years, and 47.69±9.4 years, respectively). The main cardiovascular and metabolic comorbidities associated with endometrial carcinoma were diabetes, renal lithiasis, ischemic heart disease, changes in reserve lipids, hypercholesterolemia, obesity, arterial hypertension, and the presence of varicose veins (see Table 1 for details).

The analysis of the main biological parameters found a significant difference in variance only for uric acid, glucose, urea and creatinine. All other parameters did not showed to differ significantly between the case and control groups, including cholesterol and triglycerides (see Table 2). Moreover, in all cases except blood glucose, the differences between means are of less than 15%, suggesting a low magnitude of the effect.

Discussion

Our study showed a significant association between endometrial carcinoma (Figure 2) and various cardiovascular and metabolic diseases/conditions, association previously identified by other studies as well.

Table 1 Odds ratio for endometrial cancer (* - *non-statistically significant*)

Parameter	OR	OR adjusted with age	OR adjusted with obesity	OR adjusted with age and obesity
Age	1.1			
Obesity	3.49	2.85		
Arterial hypertension	5.2	2.42	4.15	1.89
Menopause	1.26	0.62*		
Diabetes	5.1	2.17	3.89	2.75
Renal lithiasis	3.60	3.29	3.60	
Ischemic heart disease	5.71	1.7	5.50	
Changes in reserve lipids	4.1	2.6	3.00	
Varicose veins	3.27	2.13		1.75
Hypercholesterolemia	3.96	2.65	3.28	

Table 2 Main biological parameters

Uterine cancer		Uric acid	Cholesterol	Triglycerides	Glucose	Urea	Creatinine
No	Mean	4.2	207.2	105.4	97.7	28.9	0.7
	N	951.0	477.0	415.0	1187.0	1167	1191.0
	Std. Deviation	1.2	44.1	54.8	22.0	9.6	0.3
	Kurtosis	0.8	1.7	7.7	44.4	17.2	601.3
	Skewness	0.7	0.8	1.9	4.7	2.2	20.8
Yes	Mean	5.2	216.6	112.5	114.4	33.1	0.8
	N	51.0	29.0	23.0	67.0	67.0	67.0
	Std. Deviation	1.5	61.2	46.0	32.8	9.7	0.6
	Kurtosis	-1.0	0.2	9.0	16.1	-0.1	57.5
	Skewness	0.4	0.5	2.3	3.4	0.3	7.3
Total	Mean	4.3	207.8	105.8	98.6	29.2	0.7
	N	1002.0	506.0	438.0	1254.0	1234.0	1258.0
	Std. Deviation	1.3	45.2	54.3	23.0	9.7	0.3
	Kurtosis	0.7	1.5	7.7	39.6	15.8	426.1
	Skewness	0.7	0.8	1.9	4.6	2.1	17.9
Anova	F	29.8	1,2	0.365	34.1	11.8	8.1
	p	<0.001	0.28	0.546	<0.001	0.001	0.004

Menopause is associated with an increase of the OR, and subsequently relative risk for endometrial cancer. However, after adjusting these results with age, we have identified a decrease in the risk of endometrial cancer in women with an earlier menopause. This result confirms other data from the scientific literature, showing that the risk of endometrial cancer is increased in persons with early menarche or late menopause[12,13]. An increased secretion of estrogens represents the most likely reason, as estrogens are known to cause endometrial hyperplasia and afterwards endometrial carcinoma[14].

Obesity was found by our study to be an independent risk factor for endometrial cancer, the unadjusted OR being over 3, and the value of OR adjusted with age being little below 3 (see Table 1). Obesity is know to increase the risk of endometrial cancer, most likely through the generation of increased levels of estrogens secondary to the conversion androstenedione - estrone and to the aromatization of androgens to estradiol, biochemical reactions taking place in white adipocytes. Renehan et al. found that each increase with 5 kg/m^2 of the body mas index is associated with a significant increase in the relative risk for endometrial cancer (RR=1.59)[6]. Even if the risk is increased, these patients have a higher probability

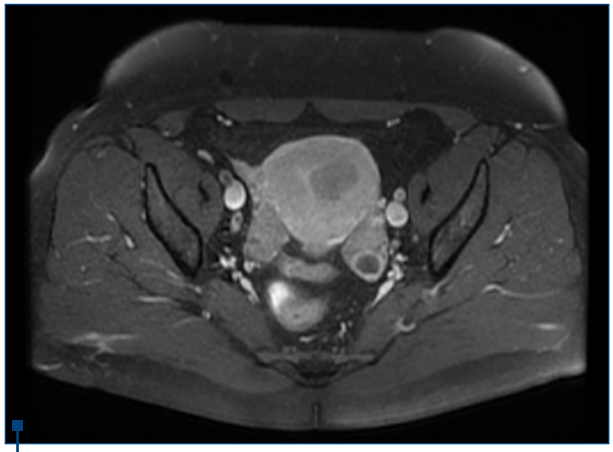

Figure 2. T2b stage endometrial tumor. Axial T1 FS C + (Gd) (post-administration contrast dye)

to have less severe forms of endometrial cancer, due to a higher probability of developing tumors responsive to estrogens, and identifiable in earlier stages[15].

Diabetes was associated with a significant increase in unadjusted OR (5.1), which decreased to 2.17 when adjusted with age and 3.89 when adjusted with obesity. These values suggest that either diabetes is an independent risk factor, or the risk is dependent on an unidentified, confounding risk variable. Similarly, blood pressure is associated with an unadjusted OR of over five (5.2), value that decreases to below 2 after adjusting it with age and obesity. These associations have been previously identified; for example Soliman et al. found that diabetes and hypertension are associated with an increased risk for endometrial carcinoma independent of obesity[7].

Ischemic heart disease is associated with a very high OR for endometrial carcinoma (over five), value that decreases severely after adjusting with age (1.7). This result seems to be in contradiction with data from the scientific literature, suggesting that estrogens have protective cardiovascular effects. Therefore, persons who synthetize increased quantities of estrogens, should have a decreased risk for cardiovascular events, including ischemic heart disease. Another possibility is that the results might be a false positive (beta error); however, this is less likely keeping in mind the magnitude of the effect. A possible explanation for the association between diabetes, hypertension and ischemic heart disease and endometrial carcinoma might be derived from particular dietary regimens. A study by Villani et al. found that the intake of lipids, proteins and glucides are higher in patients with endometrial carcinoma compared to non-neoplastic patients[16]. The authors associated this correlation with obesity; however, other studies showed increases in cancer risk associated with particular types of dietary regimes[17-19].

Renal lithiasis is associated with a threefold increase in OR for endometrial cancer. This association has been previously identified; for example Nachtigall et al. found that patients receiving hormonal substitution therapy had an increased frequency of renal lithiasis[20]. As substitution therapy is associated with an increased risk for endometrial cancer the association between these pathologies might be caused by an increased use of hormonal substitution therapy. Another possible cause for both pathologies might be diabetes, that is known to be associated with a decrease in the pH of the urine, subsequently favoring the appearance of kidney stones[21]. Obesity is also associated with kidney stones[21], but after adjusting the OR with this parameter, the value remains basically the same (3.6).

Varicose veins are associated with a threefold increase in the OR for endometrial carcinoma, value that decreases to 1.75 after adjusting it with age and obesity, two important risk factors for both pathologies. Physio-patologically the most likely cause for this association is represented by the increase in the serum levels of metaloproteinases, increase that is associated with increased estrogen levels (especially for matrix metalloproteinases (MMP) 1,2,3, 9, and 13) [22]. Moreover, MMP2 leads to venous relaxation, which causes progressive venous dilation and in time chronic venous insufficiency and varicose veins[23].

Conclusions

In conclusion, our study shows that endometrial cancer is associated with a series of cardiovascular and metabolic pathologies, associations that could not be explained by increasing age or obesity alone. The most likely cause was represented by other risk factors, common for both cardiovascular/metabolic and neoplastic diseases that should be looked for, in order to decrease the morbidity and mortality in endometrial cancer. ■

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