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GYNECOLOGIC ONCOLOGY

Overweight and obesity do not determine worst prognosis in endometrioid endometrial carcinoma

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Abstract

Purpose The aim of this study was to investigate the impact of body mass index (BMI) on disease-free survival (DFS) and overall survival (OS) in women diagnosed with EEC and treated at the Brazilian National Cancer Institute.

Methods The study comprised 849 women diagnosed with EEC who underwent surgical treatment between January, 2000 and December, 2011. The demographic and clinical characteristics of these patients were collected from medical records and their nutritional status was based on the BMI criteria. Univariate (OS and DFS) and multivariate analyses were performed using the Kaplan–Meier method and Cox proportional hazards models, respectively.

Results About 83.2% of patients were obese or overweight at time of diagnosis, with a mean BMI of 31.83. Patients were followed for an average of 34.97 months. There were 111 recurrences (13.1%) and 140 deaths (16.5%), with mean DFS of 51.90 months and mean OS of 52.25 months. There was no significant association between BMI and DFS or OS. In multivariate analysis we did not find an increased hazard of recurrence or death among overweight or obese patients.

Conclusion Overweight and obesity had no impact on EEC prognosis on the assessed cohort. Further studies are warranted.

Keywords Endometrial cancer · Obesity · Survival · Body mass index

Introduction

Endometrial cancer (EC) is the sixth most frequently diagnosed cancer among women worldwide [1]. The incidence of EC is higher in high-income countries, but it has been increasing in low- and middle-income countries. In Brazil, EC is considered the seventh most frequent tumor among women, with 6,600 new cases estimated to occur in 2018 [2].

EC is classified into two subtypes (I or II), which comprise different clinicopathological features and prognosis. Type I—endometrioid endometrial carcinoma (EEC), is the most frequent subtype and is often associated with characteristics related to good prognosis, such as low-grade, superficial myometrial invasion and early stage of disease. Type II—non-endometrioid carcinomas, comprise the minority of endometrial cancer cases, which in turn are more aggressive, diagnosed more often with metastatic disease and present poorer outcome than type I tumors [3].

The main risk factors for EC include comorbidities as diabetes mellitus and hypertension, as well as conditions associated with prolonged exposure to estrogens. These conditions are: hormone replacement therapy (HRT), chronic

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anovulation, early menarche and / or late menopause, nulliparity, and obesity [4]. Obesity is known as a risk factor for many cancers, including endometrial adenocarcinoma [5, 6]. Multiple mechanisms are probably involved in the carcinogenesis of endometrial tumor in obese patients. In the postmenopausal period, there is an increase of bioavailable circulating estrogens. These estrogens come from the aromatization of androgens in adipose tissue and from increased circulating estrogens secondary to the reduced synthesis of sex hormone binding globulin (SHBG) in the liver. Insulin resistance, hyperinsulinemia, increased secretion of adipocytokines and pro-inflammatory cytokines may also play a role in the carcinogenesis of EC [7].

Although the association between obesity and EC risk has been well established, just a few studies have investigated obesity as a prognostic factor and their findings are controversial. Some of these studies did not show any association between obesity and the risk of recurrence and cancer-related death [8–12]. Other authors observed worse survival among patients with morbid obesity, but most of the patients did not die from cancer-related causes [13, 14].

Therefore, the main objective of this study was to investigate the impact of body mass index (BMI) on disease-free survival and overall survival among women with EEC treated at the Brazilian National Cancer Institute (INCA).

Methods

The cohort included all women diagnosed with EEC in the Gynecologic Oncology Department of the Brazilian National Cancer Institute (INCA), from January 1st, 2000 to December 31st, 2011 that were followed for up to 60 months or until death. All patients with EEC confirmed by histopathology and who underwent surgery as the first therapeutic option were included. Surgery included total hysterectomy and salpingo-oophorectomy in most cases and it was considered "complete surgery" when lymphadenectomy was performed as well. Some patients did not undergo lymphadenectomy or just had vaginal hysterectomy because of obesity or serious clinical conditions (and those cases were considered "not complete surgery"). Clinical data were collected from medical records and the following variables were obtained: age at diagnosis, comorbidities report (diabetes, heart disease and hypertension), age at menarche and menopause, whether the disease was diagnosed during premenopause, treatment period, type of treatment, tumor grade and stage classified according to the International Federation of Gynaecology and Obstetrics (FIGO) [15]. Body mass index (BMI) was assessed at hospital registration prior to the treatment, and women were classified according to the categories established by the World Health Organization [16]: normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), obesity grade I (BMI 30.0–34.9 kg/m^2), obesity grade II (BMI 35.0–39.9 kg/m^2), obesity grade III (BMI $\geq$ 40 kg/m^2). There was no patient classified in the underweight group.

Recurrence was diagnosed when a new event, locoregional and/or distant, occurred during an interval of at least 6 months since the end of treatment (surgery alone or adjuvant treatment when necessary). The date of death due to any cause was obtained from the patient's death certificate. Women with non-endometrioid EC, or whose primary site of disease could not be determined, and/or those with no information about their weight and/or height at time of registration were excluded.

Exploratory analysis of the distribution variables was performed by measures of central tendency and of dispersion for quantitative variables, and absolute and relative frequency distributions for qualitative variables. To estimate disease-free survival and overall survival, cases were censored in the date of recurrence or death, respectively, or in the end of the study, whichever came first. Those cases with incomplete follow-up were censored on the date of last medical appointment.

Overall and disease-free-survival were estimated by Kaplan–Meier method and statistical significance among groups was estimated by the log-rank test. Those who remained alive at the last known follow-up were censored. Multivariate analysis was performed using the Cox proportional hazards models with stepwise forward method, comprising all variables with p value < 0.20 in univariate analysis, and with those that were related to a clinical significance that could influence the outcomes. The association between survival and the clinicopathological variables was determined by the Hazard Ratio (HR) with 95% confidence interval (CI). The variables that presented p value < 0.05 established the final model.

All analyses were performed using the SPSS statistical package (SPSS version, 20.0, Inc.—Chicago, IL-USA, 2004). This study was approved by INCA Ethics Committee and, due to the retrospective design, an abstention of the signed the Informed Consent was authorized by the Ethics Committee.

Results

A total of 912 patients were initially included in the study. Sixty three were excluded due to missing data for BMI calculation at time of hospital registration. The remaining 849 patients were included in the analysis. The mean age at diagnosis was 63.58 years (SD 10.88) and the mean BMI was 31.83 (SD 7.71) at time of EEC diagnosis. Seven hundred and six patients (83.2%) were classified as overweight or obese, with a higher proportion among women under

65 years (57.2%). Most women had hypertension (71.3%), were already postmenopausal (88.7%) and were diagnosed with early disease—FIGO stages I or II (84.2%).

Significant associations were found between earlier FIGO stages (I or II) and tumor grade (1 or 2) with higher BMI classes ($p < 0.001$ and $p = 0.002$, respectively) (Table 1). Over 25% of patients had diabetes ($n = 232$; 27.4%), a few women presented EEC before menopause ($n = 76$; 11.3%) and most of them were obese or overweight ($n = 65$; 85.5%). Most patients underwent total hysterectomy and salpingo-oophorectomy ($n = 746$; 87.9%), but lymphadenectomy was less performed in women with the highest obesity rates

Table 1 Descriptive analysis of assessed population, according to Body mass index ($n = 849$)

Variables	Body mass index at time of EEC diagnosis, *n* (%)*					
	Normal weight $n = 143$ (16.8%)	Overweight $n = 262$ (30.9%)	Obesity grade I $n = 205$ (24.1%)	Obesity grade II $n = 122$ (14.4%)	Obesity grade III $n = 117$ (13.8%)	Total
Period of treatment						
2000–2005	59 (41.3%)	104 (39.7%)	87 (42.4%)	35 (28.7%)	43 (36.8%)	328 (38.6%)
2006–2011	84 (58.7%)	158 (60.3%)	118 (57.6%)	87 (71.3%)	74 (63.2%)	521 (61.4%)
Age at diagnosis						
< 65 years	80 (55.9%)	139 (53.1%)	116 (56.6%)	74 (60.7%)	77 (65.8%)	486 (57.2%)
≥ 65 years	63 (44.1%)	123 (46.9%)	89 (43.4%)	48 (39.3%)	40 (34.2%)	363 (42.8%)
Diabetes						
No	121 (85.8%)	191 (73.2%)	137 (66.8%)	88 (72.1%)	77 (65.8%)	614 (72.6%)
Yes	20 (14.2%)	70 (26.8%)	68 (33.2%)	34 (27.9%)	40 (34.2%)	232 (27.4%)
Cardiopathy						
No	132 (94.3%)	234 (89.7%)	190 (92.7%)	109(89.3%)	105(91.3%)	770 (91.3%)
Yes	8 (5.7%)	27 (10.3%)	15 (7.3%)	13 (10.7%)	10 (8.7%)	73 (8.7%)
Hypertension						
No	69 (48.6%)	87 (33.2%)	51 (24.9%)	21 (17.2%)	15 (12.8%)	243 (28.7%)
Yes	73 (51.4%)	175 (66.8%)	154 (75.1%)	101(82.8%)	102(87.2%)	605 (71.3%)
Menarche age						
≤ 11 years	22 (22.7%)	41 (20.3%)	48 (29.8%)	28 (31.5%)	28 (28.0%)	167 (25.7%)
> 11 years	75 (77.3%)	161 (79.7%)	113 (70.2%)	61 (68.5%)	72 (72.0%)	482 (74.3%)
Menopause age						
≤ 45 years	15 (17.4%)	30 (16.7%)	27 (20.5%)	12 (15.8%)	14 (16.7%)	98 (17.6%)
> 45 years	71 (82.6%)	150 (83.3%)	105 (79.5%)	64 (84.2%)	70 (83.3%)	460 (82.4%)
Pre-menopause						
No	92 (89.3%)	193 (91.5%)	144 (86.2%)	79 (84.9%)	88 (89.8%)	596 (88.7%)
Yes	11 (10.7%)	18 (8.5%)	23 (13.8%)	14 (15.1%)	10 (10.2%)	76 (11.3%)
Lymphadenectomy						
No	45 (31.5)	85 (32.4)	84 (41.0)	57 (46.7)	85 (72.6)	356 (41.9)
Yes	98 (68.5)	177 (67.6)	121 (59.0)	65 (53.3)	32 (27.4)	493 (58.1)
FIGO staging						
I and II	100 (70.4%)	217 (82.8%)	177 (86.3%)	112(91.8%)	107(92.2%)	713 (84.2%)
III and IV	42 (29.6%)	45 (17.2%)	28 (13.7%)	10 (8.2%)	9 (7.8%)	134 (15.8%)
Tumor grade						
1 and 2	95 (66.9%)	215 (82.1%)	164 (81.6%)	98 (81.0%)	98 (83.8%)	670 (79.5%)
3	47 (33.1%)	47 (17.9%)	37 (18.4%)	23 (19.0%)	23 (19.0%)	173 (20.5%)
Chemotherapy						
No	126 (88.1)	236 (90.4)	195 (96.1)	116 (95.1)	109 (94.8)	782 (92.7)
Yes	17 (11.9)	25 (9.6)	8 (3.9)	6 (4.9)	6 (5.2)	62 (7.3)
Radiotherapy						
No	80 (55.9)	161 (62.2)	119 (58.9)	72 (59.0)	75 (64.7)	507 (60.2)
Yes	63 (44.1)	98 (37.8)	83 (41.1)	50 (41.0)	41 (35.3)	335 (39.8)

*Differences in absolute values correspond to missing data

($p < 0.001$). In all BMI categories the low-grade tumors were the most frequent. Table 1 summarizes the clinicopathological characteristics by BMI stratification.

The mean follow-up time was 34.97 months (SD 19.49). One hundred and eleven patients (13.1%) relapsed. The mean disease-free survival (DFS) was 51.90 months. In the same period of follow-up, 140 (16.5%) deaths occurred and the mean overall survival (OS) was 52.25 months. There was no significant difference on DFS ($p = 0.666$) and OS ($p = 0.833$) curves regarding the nutritional status (Table 2) (Figs. 1 and 2). No statistical differences were observed between BMI classification at time of EEC diagnosis and risk of recurrence or death in the Cox Regression, even when data were adjusted for the variables that could influence these outcomes (cancer stage, tumor grade, tumor size, hypertension, diabetes, type of surgery—complete or not, and adjuvant chemotherapy or adjuvant radiotherapy treatment) (Table 3). The OS analysis comparing patients by their cancer stage, tumor grade, hypertension, diabetes, type of surgery, and adjuvant chemotherapy or adjuvant radiotherapy treatment, according to the BMI stratification, is shown in Supplementary Table 1. Supplementary Table 2 shows the OS survival analysis stratified by BMI, considering only women diagnosed on FIGO stage I. It also demonstrated no significance among obese subgroups and normal weight patients.

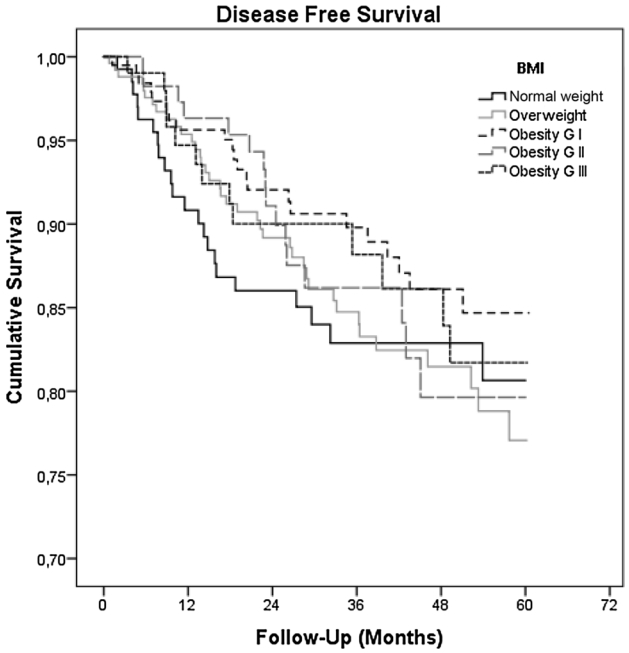

Fig. 1 Disease-free survival according to body mass index (BMI)

Discussion

According to the International Agency for Research on Cancer (IARC) and the World Cancer Research Fund (WCRF), approximately 20% of all cancer cases can be associated with obesity, especially endometrial, oesophagus (adenocarcinoma), colorectal, prostate, renal and postmenopausal breast cancers [5, 17]. Endometrial cancer was the first

Table 2 Disease-free survival and overall survival analysis by Kaplan–Meier Method, according to body mass index ($n = 849$)

Body mass index classification	Disease-free survival			
	Events (%)	Mean	CI 95% (min–max)	Log rank
Normal weight	22 (15.4%)	51.90	48.77–55.04	0.666
Overweight	38 (14.5%)	52.73	50.53–54.93	
Obesity grade I	22 (10.7%)	55.08	52.93–57.23	
Obesity grade II	16 (13.1%)	53.36	50.38–56.35	
Obesity grade III	13 (11.1%)	54.01	50.79–57.22	
Total	111 (13.1%)	53.65	52.46–54.84	
Body mass index classification	Overall survival			
	Events (%)	Mean	CI 95% (min–max)	Log rank
Normal weight	27 (18.9%)	50.64	47.43–53.85	0.833
Overweight	45 (17.2%)	51.85	49.61–54.09	
Obesity grade I	35 (17.1%)	52.56	50.10–55.02	
Obesity grade II	16 (13.1%)	53.82	50.99–56.66	
Obesity grade III	17 (14.5%)	52.97	49.67–56.28	
Total	140 (16.5%)	52.25	51.04–53.47	

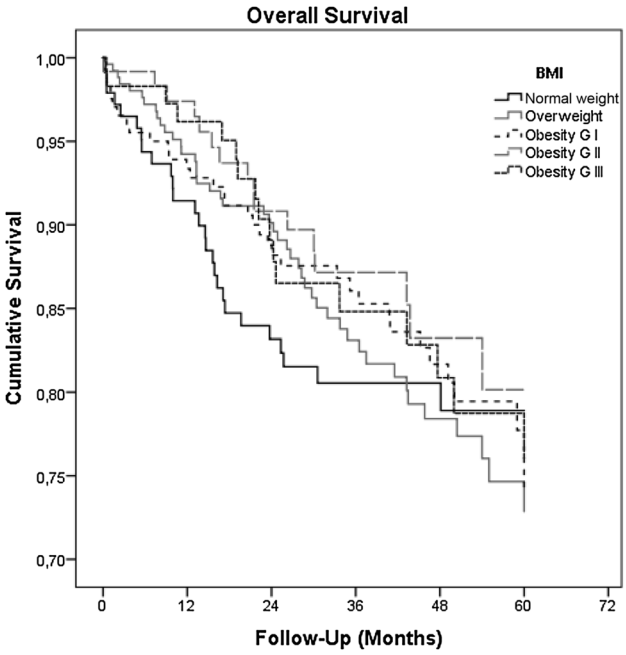

Fig. 2 Overall survival according to body mass index (BMI)

malignancy related to obesity [18] and it is estimated that obesity leads to 4.5-fold increase in risk of EC compared to non-obese women [19, 20]. Prospective studies have revealed 1.59 (95% CI 1.50–1.68) increased risk of EC for each gain of 5 kg/m^2 [6].

Although the incidence of EC is remarkable, insufficient data have addressed the impact of obesity on EC outcomes. Since about 70% of women diagnosed with EEC are obese, the consequences of obesity-related diseases should be taken into account to implement strategies to improve survival outcomes among these women [8].

A systematic review showed controversial findings of obesity as a prognostic factor for endometrial cancer patients. Four of the included studies reported a statistically significant association between obesity and higher overall mortality. However, the magnitude of association reported for endometrial cancer patients was comparable to those described in prospective studies evaluating obesity as a prognostic factor in healthy women. There was no reported association between obesity and disease-free survival [8]. Another recent meta-analysis showed an increased risk of all-cause mortality in obese endometrial cancer patients, especially those with severe obesity (BMI ≥ 40 kg/m^2) [21]. However, the studies included in this review did not investigate the outcomes according to the tumor histopathology. This fact may have biased the final results because obesity is usually associated with the risk of development of EC type I (ECC).

In addition, the majority of published studies are retrospective, consequently the patient weight and height were based on patients' verbal information or medical records. Moreover, most of them did not take into account different tumor grades and subtypes, and did not examine the

Table 3 Disease-free survival and overall survival analysis by Cox regression, according to nutritional status

Body mass index classification	Disease-free survival					
	Univariate			Multivariate*		
	HR	CI 95% (min–max)	*p* value	HR	CI 95% (min–max)	*p* value
Normal weight	Reference			Reference		
Overweight	0.987	0.584–1.668	0.960	1.668	0.917–3.034	0.094
Obesity grade I	0.683	0.378–1.234	0.207	1.477	0.745–2.928	0.246
Obesity grade II	0.873	0.458–1.663	0.679	1.709	0.811–3.605	0.159
Obesity grade III	0.808	0.407–1.604	0.542	1.352	0.609–3.002	0.555
Body mass index classification	Overall survival					
	Univariate			Multivariate*		
	HR	CI 95% (min–max)	*p* value	HR	CI 95% (min–max)	*p* value
Normal weight	Reference			Reference		
Overweight	0.961	0.596–1.549	0.870	1.332	0.770–2.304	0.276
Obesity grade I	0.895	0.541–1.478	0.664	1.777	0.986–3.201	0.056
Obesity grade II	0.710	0.383–1.318	0.278	1.208	0.602–2.426	0.595
Obesity grade III	0.847	0.462–1.555	0.592	1.017	0.502–2.061	0.962

*Adjusted for FIGO stage, hypertension, diabetes, age, tumor grade and tumor size, chemotherapy or radiotherapy adjuvant treatment, and completion surgery

association among the clinical variables and survival (the hazard ratio of relapse or death) [8, 22]. Conflicting results may also be due to the different types of studies design, lack of power and different BMI classification [21].

To our knowledge, only two previous studies have assessed the impact of obesity on survival considering histological subtypes separately with a large cohort of endometrial cancer patients. Arem et al. [23] used the Women's Health Initiative database and showed that women with EEC presented higher risk for all-cause mortality, but no significant risk for cancer-related mortality was observed; in contrast, the study conducted by Crosbie et al. [24] did not find association between obesity and survival in EEC patients, which is in accordance with our results.

Recently, some authors associated obesity in combination with metabolic syndrome with poor prognosis in patients with colorectal cancer [25]. Although our retrospective study could not provide all parameters related to metabolic syndrome, OS and DFS analysis comprising patients with and without hypertension and/or diabetes showed no significant difference among all nutritional status groups.

Importantly, we found a significant association among low-grade and early stages and severity of obesity. These findings are not well understood yet, but they are in accordance with other studies showing that obesity is often associated with lower grade, decreased stage and less indication of postoperative chemotherapy, all of which associated with a favorable prognosis [9, 24, 26–29]. This obesity paradox confirms that, despite being a risk factor for several diseases, obesity may be a protective factor for mortality in various diseases, including cancer [30].

Sedentary lifestyle and physical inactivity also seem to be relevant, and have been identified as predictors of poor prognosis in patients with different types of cancer [23]. Additionally, cancer survivors who remain physically active usually have better control of body weight and their comorbidities. Consequently, these patients have a higher quality of life than those with a sedentary lifestyle [31]. However, studies assessing the role of lifestyle (including eating, social habits and physical activity) on endometrial cancer prognosis are scarce. Prospective observational studies evaluating lifestyle behaviors before and after EC diagnosis may elucidate whether and when these factors influence clinical outcomes, including long-term survival [32].

The principal limitations of our study are due to its retrospective design, which restricts the gathering of data in relation to the quality of the information obtained. Still, it comprises a large cohort of EEC patients (the histological subtype known to be related to obesity) which provided reliable analysis and results. Similar to the previous studies mentioned above, our study had all data collected from medical records. However, the weight and height information were provided after measurement by the Nutrition Department at time of first consultation and before starting cancer treatment. Prospective studies are warranted to better understand whether obesity among women with EEC is a predictive factor of death, cancer-related death and/or recurrence, and which mechanisms are involved.

Author contributions GV Chaves: data analysis, manuscript writing/editing. TA Simão: data collection, manuscript writing/editing. LFR Pinto: protocol/project development, manuscript writing/editing. MAM Moreira: data collection, manuscript writing/editing. A Bergman: data analysis, manuscript writing/editing. CBP Chaves: protocol/project development, data collection and management, manuscript writing/editing.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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