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ORIGINAL CONTRIBUTIONS

Obesity and Cancer: the Profile of a Population who Underwent Bariatric Surgery

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Abstract

Introduction Obesity is a significant risk factor for cancer incidence and mortality. The number of patients with obesity who undergo bariatric surgery is increasing; however, the impact of such a procedure in affecting the risk of cancer is not completely understood yet.

Methods We conducted a retrospective unicentric cohort study to characterize the occurrence of cancer in patients who underwent bariatric surgery from January 2010 to December 2018. For cases of cancer identified after bariatric surgery, we performed a cancer-free survival analysis over time. We also performed a cross-sectional analysis of demographic and clinical characteristics at the time of surgery and compared patients with or without a cancer diagnosis.

Results Of the 2578 patients who underwent bariatric surgery, 117 patients (4.5%) were diagnosed with a cancer. Fifty-nine cases were diagnosed before surgery, and the remaining 58 cases occurred after the bariatric procedure. The prevalence of cancer was more accentuated in women (4.9%) than among men (2.7%). Thyroid and breast cancer were the most frequent before and after bariatric surgery, respectively. On average, patients with cancer diagnosis were older (49.0 vs 43.3 years, $p<0.001$) and with a lower level of education (7.4 vs 8.6 school years, $p=0.002$).

Conclusion Almost all the cases of cancer identified in this study were obesity-related cancers. Further prospective studies are needed to extend the current knowledge regarding the cancer risk profile of patients who undergo bariatric surgery.

Keywords Bariatric surgery · Cancer · Obesity

Key Points

•Patients with obesity are at greater risk of having cancer.
•Thyroid and breast cancer were the most frequent before and after bariatric surgery, respectively.
•Cancer risk after bariatric surgery could depend on the procedure undergone, the patient's gender, and the type of cancer.
•Further studies with long-term follow-up need to be carried out in bariatric populations.

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Introduction

As the prevalence of obesity increases globally [1], there is greater concern about the associated comorbidities and the significant burden that they represent, as obesity is a risk factor for chronic and major health problems such as cardiovascular disease, diabetes *mellitus*, musculoskeletal disorders, and cancer [2, 3].

The link between increased body mass index and carcinogenesis is nowadays supported by strong evidence [4–7]. Not only does obesity increase the morbimortality of patients with cancer, but it has also been associated with an increased risk of progression, recurrence, and death [3, 6, 8], as it is also associated with the development of a group of cancers, which have been identified in the scientific literature as obesity-related cancers [6]. According to the International Agency for Research on Cancer, this group includes esophageal adenocarcinoma; gastric cardia, colon, rectum, liver, gallbladder, pancreas, and post-menopausal breast cancer; and also endometrium, ovary, kidney renal cell, and thyroid cancer; as well as meningioma and multiple myeloma [5]. When considering the preventable causes of cancer, obesity is now the second most important cause, which is only outranked by smoking [2, 9]. Such an association highlights the importance of taking action to contain the increased number of expected cancers, as the number of people who are overweight and obese continues to grow worldwide [10].

The most effective treatment for obesity is bariatric surgery [11, 12], which results in a decrease of all-cause mortality in patients with obesity [13, 14] and promotes not only a reduction in comorbidities such as diabetes *mellitus*, dyslipidemia, nonalcoholic fatty liver disease, and obstructive sleep apnea [15, 16], but also a decrease in major cardiovascular events, including strokes and myocardial infarction [15, 17].

Published studies suggest a favorable effect of bariatric surgery in reducing all-cancers incidence and mortality [8, 11, 18, 19]. This positive effect has been notably demonstrated for some of the obesity-related cancers, such as breast and endometrial cancer [19–21], and seems to be more relevant in women [4, 22]. However, the outcomes can be different, depending on the type of surgery, the location of the cancer, and the patient's gender, as some studies present different results [20, 23–25].

Even so, the evidence regarding how cancer incidence and mortality can be affected by bariatric surgery in patients with severe obesity is still scarce, and therefore, further considerations on this matter are important, as it can influence the decision as to whether to refer a patient for bariatric surgery, or not, and it can even impact the surveillance approach to be recommended after such a procedure [26].

Our aim is to characterize the occurrence of cancer in patients who underwent bariatric surgery in our hospital and to contribute to furthering the knowledge on the cancer risk profile among patients with clinically severe obesity who are offered surgical treatment.

Methods

Study Design and Study Population

We conducted a retrospective unicentric observational cohort study, which included all patients submitted to bariatric surgery (either adjustable gastric band (AGB), Roux-en-Y gastric bypass [RYGB), sleeve gastrectomy [SG), or single anastomosis duodenal–ileal bypass with sleeve gastrectomy [SADI-S)) for the period of January 2010 until December 2018 at our hospital, a tertiary care academic hospital, which is a reference center for bariatric surgery in Portugal. All procedures were performed according to the standard technique. This cohort of patients has been followed since 2010.

Patients were evaluated by our group and were selected when they met the standard eligibility criteria for bariatric surgery, which are (a) body mass index (BMI) $\geq$ 40 kg/m^2 or BMI $\geq$ 35 kg/m^2 with at least one preoperative comorbidity; (b) aged between 18 and 65 years; (c) obesity which was not secondary to an endocrine disease; (d) non-satisfactory weight loss after at least 1 year under all appropriate non-surgical measures; (e) ability to understand the surgical procedure and to commit to a long-term follow-up plan; (f) absence of non-stabilized psychiatric disturbances or substance abuse.

Approval for the study was obtained from the Ethics Committee for Health of our hospital. All data used in this study was processed anonymously in order to safeguard patients' confidentiality.

Clinical Data Evaluated

We collected demographic, clinical, and analytical data regarding the moment when each patient underwent bariatric surgery, which included information on gender; year of birth; years of education; age at which obesity begun; year of bariatric surgery; type of bariatric surgery; weight, high, waist, and hip circumferences; and systolic (SBP) and diastolic (DBP) blood pressure. Based on these data, we were able to assess the age at surgery, the BMI, and the waist-hip ratio. We also recorded analytical information regarding plasma levels of hemoglobin A1c, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, thyroid-stimulating hormone (TSH), free thyroxine (T4), and also fasting glucose and fasting insulin, the two latter enabling us to estimate the insulin resistance by employing the homeostasis model assessment of insulin resistance (HOMA-IR) [27], using the following formula: (fasting insulin [μUI/mL] × fasting glucose [mmol/L])/22.5.

Based on the collected data, we were able to classify each patient according to the existence of metabolic syndrome defined by the presence of three or more of the following: (a) fasting plasma glucose $\geq$ 100 mg/dL; (b) SBP $\geq$ 130 mmHg and/or DBP $\geq$ 85 mmHg; (c) triglycerides $\geq$ 150 mg/dL; (d)

HDL-cholesterol < 40 mg/dL in women or < 50 mg/dL in men; and (e) waist circumference ≥ 88 cm in women or ≥ 102 cm in men [28]. The presence of hypertension, diabetes *mellitus*, dyslipidemia, or smoking was also assessed in the clinical history of each patient.

We then collected information from each patients' hospital records regarding any cancer diagnosis up to the time the study's analysis was made, namely November 2020. Whenever there was a cancer diagnosis, identified by either an ICD-10 code (International Statistical Classification of Diseases and Related Health Problems 10th Revision) or an entry in a medical record, we gathered information regarding the cancer type and its location, as well as the year when the diagnosis was made. Next, the cases of cancer were grouped according to the affected organ. Furthermore, by combining the information regarding the date of the bariatric surgery and the year of the cancer diagnosis, we were able to define whether each cancer identified took place before or after the patient was submitted to bariatric surgery.

Statistical Analysis

We performed a cross-sectional analysis of the demographic, clinical, and analytical parameters of the moment of bariatric surgery and performed three comparisons: (A) patients with *versus* without a cancer diagnosis, either before or after the bariatric surgery; (B) patients with *versus* without a cancer diagnosis before the bariatric surgery; and (C) patients with *versus* without a cancer diagnosis after the bariatric surgery. Categorical variables were expressed as proportions and were compared by using Pearson's chi-square test or Fisher exact test whenever appropriate. Continuous variables with a normal distribution were presented as mean and standard deviation (SD) and were compared using Student's *t*-test. Continuous variables with non-normal distribution were described as medians and interquartile range (IQR) and were compared using the Mann-Whitney *U* test. Missing data was not considered in the analysis.

For those cases of cancer diagnosed after bariatric surgery, we performed survival analysis, using Kaplan-Meier survival curves.

Reported *p* values are two-tailed and were considered statistically significant when $p \leq 0.05$. The statistical analyses were performed with SPSS Statistics 26® software.

Results

Between January 2010 and December 2018, 2578 patients underwent bariatric surgery and were included in the analysis. Women represented 84.4% of the patients and the mean age at the time of surgery was 43.5 years. The mean preoperative BMI was 43.8 (5.78) kg/m^2, as 74.4% of the patients had morbid obesity (BMI ≥ 40 kg/m^2). RYGB was the most frequently bariatric procedure performed. The demographic and clinical characteristics of the study population are summarized in Table 1.

Among the study population, 117 patients (4.5%) had been diagnosed with cancer before this study was carried out. The prevalence of cancer was higher among women (4.9%) than among men (2.7%). Fifty-nine cases were diagnosed before surgery, and the remaining 58 cases occurred after the bariatric procedure.

Figures 1 and 2 describe the distribution of the cases of cancer, by gender and cancer location, among patients who were diagnosed with cancer before or after undergoing bariatric surgery, respectively.

Cancer prior to surgery was diagnosed in 2.5% of women (54/2176) and 1.2% of men (5/402). The mean age at diagnosis was 38.5 (9.43) years. The most frequent cancer diagnosed before bariatric surgery was thyroid cancer, with 27 cases (45.8%), followed by breast cancer (32.2%), and colorectal cancer (8.5%).

Cancer after bariatric surgery was diagnosed in 2.4% of women (52/2176) and 1.5% of men (6/402). The mean age at diagnosis was 49.4 (9.71) years. The most frequent cancer in this group was breast cancer, with 24 cases (41.4%),

Table 1 Demographic and clinical characteristics of the study population (n = 2578).

Variable	
Female gender, *n* (%)	2176 (84.4)
Age, years*	43.5 ± 10.69
School years, years*	8.6 ± 3.50
BMI, kg/m^2*	43.8 ± 5.78
Obesity grade, *n* (%)	
Overweight (BMI of 25.0 to 29.9 kg/m^2)	4 (0.2)
Class I obesity (BMI of 30.0 to 34.9 kg/m^2)	65 (2.6)
Class II obesity (BMI of 35.0 to 39.9 kg/m^2)	581 (22.9)
Class III obesity (BMI of 40.0 kg/m^2 or higher)	1890 (74.4)
Bariatric surgery, *n* (%)	
AGB	272 (10.6)
RYGB	1503 (58.3)
SG	802 (31.1)
SADI-S	1 (0.0004)
Hypertension, *n* (%)	964 (39.6)
Diabetes mellitus, *n* (%)	562 (22.9)
Dyslipidemia, *n* (%)	536 (21.9)
Metabolic syndrome, *n* (%)	885 (34.3)

BMI body mass index, *AGB* adjustable gastric band, *RYGB* Roux-en-Y gastric bypass, *SG* sleeve gastrectomy, *SADI-S* single anastomosis duodenal–ileal bypass with sleeve gastrectomy

*Values are shown as mean ± standard deviation

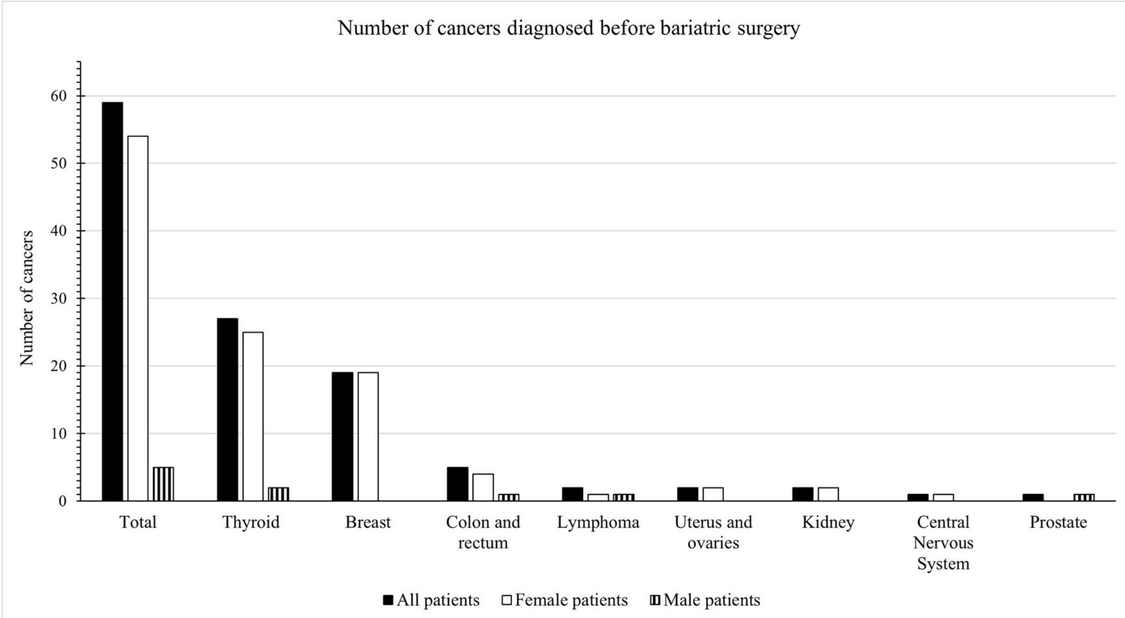

Fig. 1 Number of cases of cancer diagnosed before bariatric surgery—total and by cancer location, for both females and males.

followed by uterus and ovarian cancer (17.2%), and then thyroid and colon and rectum cancer, with equal prevalence (10.3%).

For the cases of cancer diagnosed after bariatric surgery, the survival analysis showed that half of the cases of cancer occurred before the fourth year after bariatric surgery and that all cases occurred up until the ninth year. The Kaplan-Meier curve representing the cumulative proportion of cancer-free survival over the years after bariatric surgery is shown in Fig. 3.

The results from the cross-sectional analysis, which consider demographic, clinical, and analytical parameters evaluated by the time of bariatric surgery, are reported in Table 2.

In analysis A, the patients diagnosed with cancer were older (49.0 vs 43.3 years, p<0.001) and had a lower level of education (7.4 vs 8.6 school years, p=0.002). In this analysis, when compared to patients without a diagnosis of cancer, those patients with cancer had a greater frequency of hypertension (51.8 vs 39.0%, p=0.008) and higher median levels of hemoglobin A1c (5.70 vs 5.60, p=0.005), as well as levels of T4 (median 1.07 vs 1.01 μg/dL, p=0.001).

In turn, in analysis B, which only considered patients who had been diagnosed with cancer before bariatric surgery, these patients were older (49.0 vs 43.4 years, p<0.001), had a lower level of education (8.0 vs 9.0 school years, p=0.050), and lower BMI on average (42.0 vs 43.8 kg/m^2, p=0.020).

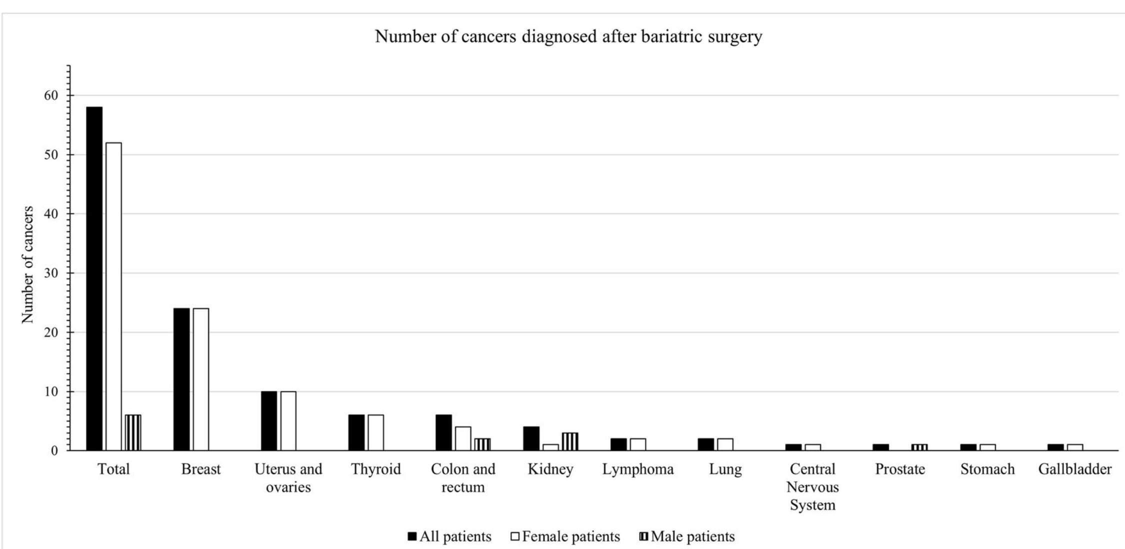

Fig. 2 Number of cases of cancer diagnosed after bariatric surgery—total and by cancer location, for both females and males.

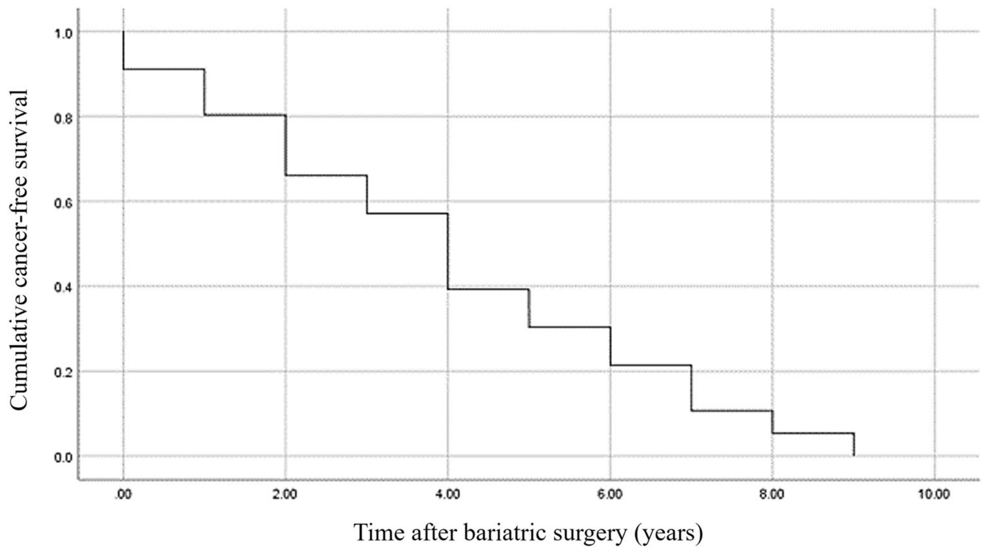

Fig. 3 Kaplan-Meier curve of cancer-free survival for the years following bariatric surgery in the group of patients who were diagnosed with cancer after undergoing bariatric surgery.

Patients with cancer presented higher levels of hemoglobin A1c (5.80 vs 5.60%, p=0.009) as well as higher levels of T4 (1.09 vs 1.01 μg/dL, p=0.001), while levels of TSH were lower (1.52 vs 1.78 μg/dL, p=0.043) when compared to patients without a cancer diagnosis before surgery.

In analysis C, which accounted for patients who were diagnosed with cancer after having undergone bariatric surgery, these patients were older (49.1 vs 43.4 years, p<0.001), had a lower level of education (7.0 vs 8.6 school years, p=0.005), and had a higher prevalence of hypertension (57.1 vs 39.2%, p=0.010) when compared to patients without a cancer diagnosis after surgery.

Even though RYGB was the most frequent bariatric procedure performed, regardless of whether we consider patients with or without a cancer diagnosis, a statistically significant difference existed for the distribution of patients by type of bariatric procedure in analyses A (p=0.002), B (p=0.024), and C (p=0.001).

Discussion

Through this retrospective unicentric observational cohort study we were able to identify 117 cases of cancer among a population of 2578 patients (4.5%) who underwent bariatric surgery.

Most of our study population (84.4%) were women, which is similar to that reported in other studies carried out on patients submitted to bariatric procedures [19, 29].

The most frequent cancers diagnosed before bariatric surgery were thyroid cancer, breast cancer, and colon and rectum cancer. When considering those cases that occurred after surgery, breast cancer was the most frequent, followed by uterus and ovaries cancer, and then thyroid and colon and rectum cancer. The distribution of type of cancer cases identified in our study population was different from the data of the 2020 Global Cancer Observatory, which described the most frequent cancers in the Portuguese population as being colorectum, breast, prostate, lung, and stomach cancer [30]. However, this difference could be explained by the age range and gender distribution of the patients included in our study. When considering data from an oncologic regional report for 2017, the most frequent cancers in the age group of 40 to 49 years were breast, colon and rectum, and thyroid cancer [31], which is in agreement with our results. Females presented a higher prevalence of cancer than males in our population (4.9 vs 2.7%), this difference also being in accordance with the data from the abovementioned oncologic regional report [31], which is in agreement with a recent narrative review performed by Castagneto-Gissey et al., which highlights a greater BMI-related risk of cancer in women [4].

Almost all (91.4%) cases of cancer identified in our study are included in the group of obesity-related cancers [5], which suggests that obesity could indeed be a key factor for the development of cancer in our study population.

There is now strong evidence in the literature supporting the hypothesis that obesity is a risk factor for cancer [4, 6]. The proposed mechanisms comprise (a) insulin resistance and hyperinsulinemia, which increases anabolism and insulin-like growth factor 1, which has been recognized to promote tumor growth [4, 7, 32]; (b) hyperglycemia and dyslipidemia, which contribute to oxidative stress [4, 32]; (c) higher levels of circulating estrogens, which promote tumor progression of hormone-sensitive tumors [4, 33, 34]; (d) chronic inflammation, with the release of pro-inflammatory molecules and immunologic dysregulation, which contributes to a favorable microenvironment for the growth, progression, and migration of tumor cells [4, 35]; (e) decreased levels of adiponectin, which has an anti-proliferative effect if the levels are normal [3]; and (f) changes in gut microbiome, which contributes to a

Table 2 Comparison of demographic, clinical, and analytical characteristics at the time of bariatric surgery, between: (A) all patients diagnosed with cancer (before or after bariatric surgery) *versus* patients with no cancer diagnosis; (B) patients diagnosed with cancer before bariatric surgery *versus* those who were not; (C) patients diagnosed with cancer after bariatric surgery *versus* those who were not.

Variable	A			B			C		
	No cancer	With cancer	*p* value	No cancer before surgery	With cancer before surgery	*p* value	No cancer after surgery	With cancer after surgery	*p* value
Female gender, *n* (%)	2070 (84.1)	106 (90.6)	0.078	2122 (84.2)	54 (91.5)	0.179	2123 (84.3)	53 (89.8)	0.362
Age, years*	43.3 ± 10.68	49.0 ± 9.43	**<0.001**	43.4 ± 10.70	49.0 ± 8.59	**<0.001**	43.4 ± 10.67	49.1 ± 10.25	**<0.001**
Age of obesity onset, *n* (%)									
< 10 years	718 (35.6)	25 (28.4)	0.354	732 (35.5)	11 (25.0)	0.249	729 (35.4)	14 (31.8)	0.306
≥ 10 and ≤ 20 years	315 (15.6)	14 (15.9)		319 (15.5)	10 (22.7)		325 (15.8)	4 (9.1)	
> 20 years	984 (48.8)	49 (55.7)		1010 (49.0)	23 (52.3)		1007 (48.9)	26 (59.1)	
School years*	8.6 ± 3.48	7.4 ± 3.63	**0.002**	9.0 (IQR 6.0)	8.0 (IQR 8.0)	**0.050**	8.6 ± 3.49	7.0 ± 3.81	**0.005**
Bariatric surgery, *n* (%)									
AGB	250 (10.2)	22 (18.8)	**0.002**	265 (10.5)	7 (11.9)	**0.024**	256 (10.2)	16 (27.1)	**0.001**
RYGB	1442 (58.6)	61 (52.1)		1473 (58.5)	30 (50.8)		1472 (58.4)	31 (52.5)	
SG	769 (31.2)	33 (28.2)		781 (31.0)	21 (35.6)		790 (31.4)	12 (20.3)	
SADI-S	0 (0.0)	1 (0.9)		0 (0.0)	1 (1.7)		1 (0.0)	0 (0.0)	
Body mass index, kg/m^2*	43.8 ± 5.79	42.9 ± 5.60	0.089	43.8 ± 5.78	42.0 ± 5.57	**0.020**	43.8 ± 5.79	43.7 ± 5.51	0.726
Waist circumference, cm*	122.8 ± 13.48	121.6 ± 11.68	0.405	121.0 (IQR 17.0)	118.5 (IQR 19.8)	0.087	122.8 ± 13.46	124.0 ± 10.41	0.313
Hip circumference, cm*	132.0 ± 11.75	131.5 ± 10.99	0.734	131.0 (IQR 15.0)	129.0 (IQR 15.3)	0.511	131.9 ± 11.75	132.6 ± 10.24	0.654
Waist-hip ratio*	0.93 ± 0.09	0.92 ± 0.08	0.533	0.93 ± 0.09	0.91 ± 0.09	0.243	0.9 ± 0.09	0.9 ± 0.07	0.583
HOMA-IR*	4.1 (IQR 3.60)	3.7 (IQR 2.42)	0.235	4.1 (IQR 3.58)	3.8 (IQR 3.28)	0.873	5.1 ± 4.28	3.6 ± 2.17	0.061
Smoking, *n* (%)	325 (15.3)	8 (8.1)	0.070	329 (15.1)	4 (7.5)	0.183	329 (15.1)	4 (8.5)	0.299
Hypertension, *n* (%)	906 (39.0)	58 (51.8)	**0.008**	937 (39.4)	27 (47.4)	0.283	932 (39.2)	32 (57.1)	**0.010**
Diabetes *mellitus*, *n* (%)	529 (22.6)	33 (29.5)	0.118	547 (22.9)	15 (25.9)	0.707	543 (22.7)	19 (34.5)	0.057
Dyslipidemia, *n* (%)	511 (21.9)	25 (22.1)	0.999	523 (21.9)	13 (22.4)	0.999	523 (21.9)	13 (23.2)	0.942
Metabolic syndrome, *n* (%)	846 (34.4)	39 (33.3)	0.895	866 (34.4)	19 (32.2)	0.834	865 (34.3)	20 (33.9)	0.999
HbA1c, %*	5.60 (IQR 0.70)	5.70 (IQR 1.1)	**0.005**	5.60 (IQR 0.70)	5.80 (IQR 0.80)	**0.009**	5.85 ± 1.02	6.22 ± 1.45	0.167
Total cholesterol, mg/dL*	196.0 (IQR 50.0)	201.0 (IQR 50.0)	0.378	196.0 (IQR 50.0)	201.0 (IQR 52.0)	0.873	197.8 ± 38.90	202.7 ± 35.63	0.293
LDL-cholesterol, mg/dL*	121.0 (IQR 43.0)	124.0 (IQR 41.0)	0.257	121.0 (IQR 43.0)	121.0 (IQR 40.5)	0.449	122.1 ± 33.05	125.8 ± 31.61	0.431
HDL-cholesterol, mg/dL*	48.0 (IQR 14.0)	49.0 (IQR 15.0)	0.761	48.0 (IQR 14.0)	50.0 (IQR 14.0)	0.083	49.9 ± 12.48	47.9 ± 10.41	0.241
TG, mg/dL*	122.0 (IQR 76.0)	121.0 (IQR 58.0)	0.800	122.0 (IQR 76.0)	116.5 (IQR 63.0)	0.192	139.1 ± 81.68	139.4 ± 54.45	0.309
T4, μg/dL*	1.01 (IQR 0.19)	1.07 (IQR 0.26)	**0.001**	1.01 (IQR 0.19)	1.09 (IQR 0.34)	**0.001**	1.02 ± 0.15	1.07 ± 0.19	0.143
TSH, μg/dL*	1.78 (IQR 1.25)	1.68 (IQR 1.88)	0.264	1.78 (IQR 1.26)	1.52 (IQR 2.40)	**0.043**	2.1 ± 2.66	2.1 ± 1.30	0.792

AGB adjustable gastric band, *RYGB* Roux-en-Y gastric bypass, *SG* sleeve gastrectomy, *SADI-S* single anastomosis duodenal–ileal bypass with sleeve gastrectomy; waist-hip ratio, the relation between waist and hip circumferences; HOMA-IR, insulin resistance determined by the homeostasis model assessment of insulin resistance; *HbA1c* hemoglobin A1c, *LDL-cholesterol* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *TG* triglycerides, *T4* free thyroxine, *TSH* thyroid-stimulating hormone

*Values are shown as mean ± standard deviation or median (IQR, interquartile range) metabolic dysregulation which is favorable for tumor growth and a state of subclinical inflammation [4, 36, 37].

The cross-sectional analysis showed some differences between patients with or without a diagnosis of cancer. Cancer patients were older and had a lower level of education, which could be related with the fact that the risk of cancer increases with age [1, 2] and that lower education is associated with a higher prevalence of obesity [2], or even that a lower socioeconomic level represents a risk factor for worse health outcomes [1].

Patients who had been diagnosed with cancer before surgery had lower mean BMI—which can be partly explained by the fact that a diagnosis of cancer could have promoted changes regarding a healthier lifestyle which could precipitate a decrease in the BMI, although this would not explain the higher level of hemoglobin A1c also found in those patients—which translates into a sustained state of hyperglycemia. As mentioned above, hyperglycemia is one of the mechanisms which is proposed to explain the obesity-related risk of cancer [4, 32] and is thus expected to be evident in this group of patients. In the group of patients who were diagnosed with cancer after undergoing bariatric surgery, the level of hemoglobin A1c also tended to be higher, albeit without a statistically significant difference.

The differences in the hormones related to thyroid function among patients who had been diagnosed with cancer before bariatric surgery can be explained by the fact that patients who had thyroid cancer (which account for 45.8% of this group) may have to suppress the levels of TSH as part of their treatment—which justifies the lower level of TSH in this group; such suppression is achieved by treatment with exogenous T4 hormone—which can explain the higher levels of T4 that was also found in this group.

Patients who had been diagnosed with cancer after bariatric surgery had higher prevalence of hypertension—which could represent a higher comorbidity burden and metabolic dysregulation for this group who also presented a higher prevalence of diabetes *mellitus*, dyslipidemia, and metabolic syndrome, albeit not significant. Unhealthier metabolic individuals are at higher risk of cancer development [4], and thus, such a difference could be expected in this group.

When considering the bariatric procedures performed, the RYGB was the most frequent type of surgery, both in patients with and without a cancer diagnosis. Nevertheless, there was a statistically significant difference in our results concerning the distribution of patients by type of surgery when comparing patients with a cancer diagnosis to those without, in analyses A, B, and C. In general, our results showed a tendency to a higher frequency of ABG and slight lower recurrence of RYGB and SG in patients who have a cancer diagnosis when compared to those who have not. Such difference is more significant for the patients who were diagnosed with cancer after the bariatric surgery, who presented the higher prevalence of AGB. It is important to consider that the majority of AGB were performed during the first years of the time period covered by this study, and therefore, these patients are now older and thus more at risk of having cancer. We can also hypothesize that as AGB is a less effective procedure [16], these interventions could have been less effective in terms of weight loss, and thus, such patients could have maintained higher levels of BMI for a longer period of time—which would thus contribute to a greater cancer risk.

The trend nowadays has been for an increasing number of SG and RYGB interventions—which currently account for all the bariatric procedures performed in our hospital. This change of practice is in line with the most recent scientific evidence—which demonstrates better results with RYGB and SG in terms of BMI-reduction [16].

The results from our cancer-free survival analysis also deserve some considerations. The median survival occurred between the third and fourth year after surgery. Considering that carcinogenesis is usually a protracted process over time, we could expect bariatric surgery to have a relatively small impact among the cancer cases which occur during the early follow-up time after the procedure, especially the ones that took place during the first post-surgery year, as the development of those cancers is likely to have started months, or even years before the patient underwent bariatric surgery. Accordingly, we can question whether the five cases that occurred during the first year are more similar to those that occurred before bariatric surgery, rather than those that occurred afterwards.

When considering the cases of breast cancer, further discrimination as to whether the cases happened before or after menopause would be important as the evidence suggesting a protective effect from bariatric surgery has been stronger for post-menopausal cases and a recent study by Feigelson et al. (2020) also suggests that there may exist different mechanisms underlying the carcinogenesis of pre- *versus* post-menopausal breast cancers [38].

In general, the existing data on bariatric surgery and cancer supports the hypothesis of a reduction in all-cancer risk and mortality [11, 18, 19]. The results are even more significant in obesity-related cancers [4, 19, 23], and the effect tends to be greater among women in most studies [4, 22]. Over the past years, several studies have attempted to understand the effect of bariatric procedures on specific types of cancer, and a beneficial effect has already been demonstrated for cancers such as breast cancer [8, 38–40] or endometrium cancer [8, 23, 33, 39]. Besides the impact on cancer development, some studies have also raised the hypothesis that bariatric surgery can improve cancer prognosis in patients with severe obesity [20, 41].

One of the unsolved questions concerns the doubt regarding whether the anatomical, physiological, and microbiome changes induced by bariatric surgery in the gastrointestinal tract lead to an increase in the risk of cancer in this location

[26, 42]. For it is known that the onset of esophagogastric cancer has been reported in some cases after bariatric surgery, although this does not provide sufficient evidence to allow any definite conclusions [43, 44]. On the other hand, colorectal cancer has been a source of contradiction in the scientific literature for some time now, as several studies have showed a beneficial effect of bariatric surgery [45, 46], while others have shown no effect [8, 25], and some studies have even suggested an increase in colorectal cancer risk after undergoing bariatric surgery [23, 26, 47, 48]. To add further to this uncertainty, the effect of bariatric surgery could well be different, depending on whether we are considering colon or rectum carcinogenesis [19, 24, 26, 45].

Our study does not enable us to draw any conclusion regarding this issue of a relation with gastrointestinal cancer, as the maximum time period under study in our analysis was from 2010 to 2020, with the period being even shorter for the majority of those patients who were consecutively submitted to surgery within that time range. The development of premalignant lesions and their progression to an invasive cancer takes several years, whether the location be esophagogastric or colorectal [43, 46]. From a medium-to-long-term perspective, the effect of bariatric surgery on either reducing or increasing the risk of cancer needs to be better evaluated, with a longer follow-up time and a contemporaneous comparative group of patients with equivalent obesity and other cancer risk factors profile who have not been submitted to surgical treatment for their obesity. In such a study, it would also be important to consider that those patients who undergo bariatric surgery are probably more likely to participate in cancer screenings or to agree to increased medical surveillance [46]—which would make the identification of cancer at an early stage more likely—which would contribute to improving the prognosis. It is thus important to study not only the number of cases, but also their prognosis and rates of mortality.

The current study presents certain limitations which are important to consider. As this is a retrospective study, the quality of the information collected is affected by several error and bias sources, such as errors of codification, missing data, follow-up losses, or the use of health care services from other hospitals, whose data we were either unable to access or it might not have been reported by patients. This information bias could have led to an underestimation of the cancer diagnosis. In addition, the fact that only 15.6% of our study population were men makes it harder to estimate the cancer risk profile for the male gender. Furthermore, the lack of a control group limits our ability to formulate hypotheses concerning the potential effect of bariatric surgery on cancer risk. It is also important to consider that not all patients with obesity, even not all patients with morbid obesity, are referred for bariatric surgery—which represents a selection bias, as patients who are referred for surgery are likely to possess different characteristics to those who are not referred for surgery, in terms of severity of obesity and its comorbidities, lifestyle behaviors, access to health services, and socioeconomic level. This selection bias could have led to the misinterpretation of our results—for instance, patients with a recent, severe, or ongoing cancer would be less likely to be referred for bariatric surgery, or even excluded from such procedures, which would consequently lead to the underestimation of the number of cancer cases before surgery.

Nevertheless, this study also presents strengths. For instance, it is possible to compare or generalize our results with those of other bariatric surgery populations, as our study included all those patients who underwent bariatric surgery in our hospital, without introducing a selection bias with exclusion criteria. Another positive aspect of the design of our study is the fact that all the patients in the study are from the same hospital and were therefore all referred for surgery based on the same criteria and were submitted to bariatric procedures by the same technical standards, which reduces the probability of potential confounders.

This study also raised some considerations which we believe should be taken into account in future research. For example, it would be important to explore the effect of bariatric surgery on the risk of cancer over the years after surgery and also to identify the moment when such risk starts to be influenced by the metabolic, endocrine, and other post-surgical alterations. To be able to achieve a more complete and clear interpretation of the specific impact of the bariatric procedure, not only is a non-surgery control group required, but also information regarding the evolution of BMI over the years after bariatric surgery. We would also like to highlight the need for studies with a longer follow-up time, and preferably with a prospective design to minimize information bias.

As mentioned above, there are still some unanswered questions [4] regarding the possible impact of bariatric surgery on the risk of cancer in patients with obesity which regards not only the effect of the surgery itself, but also that of those underlying mechanisms [4] which could differ when considering distinct bariatric procedures [4, 45], different gender [4, 19, 49], or particular cancer locations and subtypes [8, 23, 25]. Such information could influence the decision-making process regarding whether or not to refer a patient for bariatric surgery, according to their individual risk and it could also interfere with the surveillance strategy of follow-up after these procedures.

As the prevalence of obesity is expected to continue to increase over the coming years [10] and as bariatric procedures have proven to be safe and effective [50], we can only expect the number of patients with obesity who are offered surgical treatment to grow as a result. These considerations advocate the need to carry out further research to extend the current knowledge regarding the cancer risk profile of patients who undergo bariatric surgery.

Conclusion

Almost all the cases of cancer identified in this study population were obesity-related cancers. The most frequent cases were breast cancer, thyroid cancer, and uterus and ovarian cancer, followed by colorectal cancer. Thyroid cancer was the most frequent when considering just those cases that occurred before submission to bariatric surgery. Those patients who were diagnosed with cancer were older and possessed a lower level of education. There is a need to carry out prospective studies on bariatric surgery populations—preferably with a more extensive follow-up time—in order to better estimate the risk of cancer among patients with obesity who are offered surgical treatment.

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Declarations

Ethics Approval For this type of study, formal consent is not required.

Informed Consent Informed consent does not apply.

Conflict of Interest The authors declare no competing interests.

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