*Obesity Surgery, **15**, 1171-1176*

Prevalence of Cancer in Italian Obese Patients Referred for Bariatric Surgery

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Background: An association between obesity and cancer has been shown in large epidemiological studies. The aim of this study was to evaluate the prevalence and types of malignancies in an Italian cohort of obese patients referred to a bariatric center.

Methods: A retrospective, observational study was conducted. Between Jan 1996 and Dec 2004, 1,333 obese patients (M=369, F=964) were seen in the center for minimally invasive treatment of morbid obesity. Morbid obesity were considered as BMI >40 kg/m^2 or BMI >35 kg/m^2 with at least one co-morbidity. Obese and morbidly obese patients who suffered any form of cancer were reviewed.

Results: 43 patients (3.2%) presented various malignancies, with 88.3% in females. The prevalence of cancer in the younger group (21-46 years) was higher than in the older group (47-70 years), 2.1% vs 1.1%. 26 obese patients out of the 43 (60.5%) (age 41±7.9 years, BMI 38.2±9.9) presented hormone-related tumors. The most frequent site of cancer was breast (20.9%), followed closely by thyroid.

Conclusion: This is the first Italian report on prevalence of cancer in a homogeneous obese population attending an academic bariatric center. The morbidly obese patients appear to have a higher risk of developing cancer, with a higher prevalence of hormone-related tumors. The predominant gender affected by both obesity and cancer was female. Thus, a preoperative work-up for cancer screening is indicated in this group of patients.

Key words: Morbid obesity, obesity, cancer, hormone-related tumors, bariatric surgery

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Introduction

An association between obesity and cancer has been found in large epidemiological studies.[1-3] An increased prevalence of cancer of the endometrium, kidney, gallbladder and postmenopausal breast in women, and of the colon, esophagus, gallbladder and prostate in men, has been reported in obese patients.[3-9] For other sites (liver, pancreas, stomach, thyroid, lung, hematopoietic cancers), an association has been indicated, although the risk of higher prevalence is still under investigation.[2-3,10-13]

The explanation for the increased risk of cancer in the obese population is not completely known. Elevated plasma estrogen levels and a relative hyperandrogenism are hypothesized to be the reason for an increased risk for hormone-related tumors, as well as increased exposure to insulin and insulin-like growth factor I (IGF-I). The influence of excess body weight on the risk of death from cancer has been studied in a population of more than 900,000 U.S. adults (404,576 men and 495,477 women); in both sexes, the BMI was directly associated with higher rates of death from cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas and kidney.[2]

The prevalence of obesity increases with age to a maximum peak between 45-64 years, with women having higher levels of obesity and morbid obesity.[9] In Italy, obesity has shown a continuous positive trend in the last decades. Currently, obese Italians represent 9.1% of the total population,[14] with an equal distribution between genders. The highest per-

centile of the obese population is 55-64 years of age (15%), closely followed by the 45-54 years age-group. Mortality from cancer in Italy is 9.4 per 1,000 inhabitants, responsible for 154,618 deaths in 2000.[15] Breast is the most frequent cause of death from cancer in women,[15] with 35,000 new cases/year.[16] The aim of this study was to ascertain the prevalence and types of malignancies in an Italian morbidly obese population referred to a bariatric center.

Methods

A retrospective study was conducted based on a review of the Center of Minimally Invasive Treatment of Morbid Obesity database, Policlinico Umberto I, Rome. From Jan 1996 to Dec 2004, 1,333 consecutive obese patients (M=369, F=964) were observed. Subjects were classified according to the FAO/WHO/UNU criteria[16] into overweight (BMI 25-29.9 kg/m^2), grade I obese (BMI 30-34.9 kg/m^2) and grade II obese subjects (BMI 35-39.9 kg/m^2). Morbidly obese patients were those with BMI >40 kg/m^2 or >35 with at least one of the co-morbidities listed in Table 1.

All candidates for bariatric surgery underwent preoperative work-up which included physical examination, routine laboratory tests, endocrinologic, nutritional and psychiatric evaluation, chest X-ray, upper GI endoscopy, abdominal and thyroid ultrasound, and electrocardiogram. A total of 964 morbidly obese patients received different minimally invasive bariatric procedures (Table 2). All treated patients attended a follow-up program. Clinic visits were carried out at 1, 3, 6 and 12 months after surgery in the first year and every 6 months afterwards. The follow-up included clinical evaluations (surgeon, psychiatrist, nutritionist), routine laboratory tests, barium swallow (every 6 months for the first year, once per year thereafter), and upper GI endoscopy (once per year).

Patients with a cancer history 5 years before their first bariatric visit or suspected of malignancy during preoperative work-up completed their investigations with more specific tests according to the malignancy site: tumor markers, mammogram, thyroid fine-needle aspiration, imaging studies (ultrasound examination, computed-tomography scan, magnetic resonance, etc.).

Statistical Analysis

Data are expressed as percent (%) and mean ± standard deviation (SD). The database of the Center of Minimally Invasive Treatment of Morbid Obesity was reviewed. Data had been collected and recorded using the FileMaker Pro 6 database program (FileMaker Inc, Santa Clara, CA, USA). The prevalence of cancer in the 1,333 obese subjects was calculated. Because of the small number of patients with the diagnosis of cancer, the prevalence by age was calculated in two age-groups: 21-46 and 47-70 years. Unpaired *t*-test with 95% confidence interval (CI) was applied to evaluate the differences between

Table 1. Co-morbidities presented in 1,333 obese patients

Co-morbidities	Patients (%)
Hypertension	383 (28.7%)
Type 2 diabetes	125 (9.3%)
Impaired glucose tolerance	165 (12.3%)
Dyslipidemia	265 (19.8%)
OSAS	154 (11.5%)
Hyperuricemia	67 (5.0%)
Degenerative joint disease	220 (16.5%)
Chronic venous insufficiency	124 (9.3%)
Cholelithiasis	43 (3.2%)

Hyperglycemia=impaired fasting glucose 110-126 mg/dL; hyperinsulinemia=fasting insulin >25 μU/L; OSAS=obstructive sleep apnea syndrome

Table 2. Minimally invasive bariatric treatment in 964 morbidly obese patients

No. of patients	Treatment	Mean BMI (kg/m^2)	Mean age (range) (years)
384	LAGB	43.1 ± 5.1	42 (21-65)
104	LAP-GBP	47.1 ± 4.7	43 (21-66)
47	LAP-BPD-DS	56.6 ± 8.6	42 (19-64)
429	BIB	41.2 ± 9.4	37.5 (18-64)

LAGB = laparoscopic adjustable gastric banding; LAP-GBP = laparoscopic gastric bypass; LAP-BPD-DS = laparoscopic biliopancreatic diversion with duodenal switch; BIB = BioEnterics intragastric balloon

variables. A two-tailed $P<0.05$ indicated statistical significance. The analysis was done using GraphPad Software (San Diego, CA, USA).

Results

The BMI distribution in the 1,333 patients is shown in Figure 1. BMI ranged from 30 to 82 kg/m^2, and age ranged from 18 to 70 years. Morbid obesity was present in 1,045 of the obese patients. Forty-three (3.2%) of the 1,333 obese patients (mean age 48.3±10.1 years and mean BMI 43.9±6.8 at first bariatric visit) presented different forms of malignant tumors. The predominant gender was female (88.3%). The site-specific prevalence of malignant disease in this cohort is reported in Table 3.

The prevalence of cancer in the two age-groups (21-46 and 47-70 years) in the 1,333 obese patients is reported in Figure 2.

The younger group showed a higher prevalence of cancer (2.1% vs 1.1%) and lower BMI than the older group (35.28±7.8 vs 42.9±8.48, $P< 0.05$, 95% CI -12.7 to -2.8).

We classified the 43 patients with cancer into 3 subgroups: group A, patients treated for cancer before requiring treatment for morbid obesity; group B, patients diagnosed with malignant disease during the preoperative work-up for bariatric surgery; and group C, patients diagnosed with cancer during the follow-up after bariatric surgery.

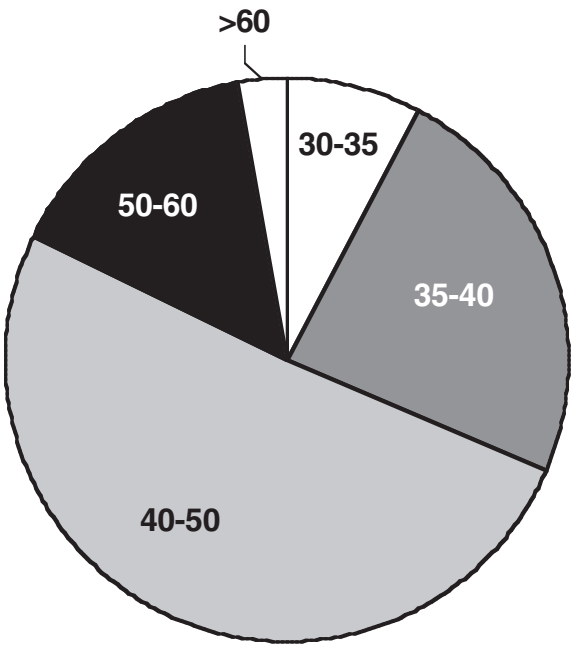

Figure 1. Distribution of BMI in the 1,333 obese patients.

Group A: 31 patients (72.8%) were diagnosed and treated for their malignancies *before* the bariatric surgeon visit, and 27 (87.1%) were female. Mean age, BMI and waist-hip ratio (WHR) at cancer diagnosis had been 40.6 ± 8.8 years, 35.6 ± 7.8 kg/m^2 and 0.91 ± 0,065, respectively. Mean interval between surgery for cancer and the first visit for bariatric surgery was 9.8 years.

Group B: Nine malignancies (20.1%) were discovered *during* the preoperative work-up or intraoperatively. Mean age, BMI and WHR at cancer diagnosis was 44.9 ± 12.7 years, 47.1 ± 7.6 kg/m^2 and 0.96 ± 0.086, respectively.

Once the diagnosis was made, these patients underwent more specific investigations as indicated: blood tests, fine-needle aspiration for suspected thyroid cancer, and abdominal CT scan for gastric adenocarcinoma, gastric GIST (GI stromal tumors) and adrenal adenocarcinoma, hematological consultation and specific blood tests for multiple myeloma. Afterwards, these patients received appropriate treatment (Table 4).

Group C: Three of the 43 "cancer" patients (7%) developed malignant disease at a mean of 4.6 years *after* bariatric surgery, with the diagnosis established at the scheduled follow-up visit. Mean age, BMI and WHR at bariatric surgery were 39.6 ± 10.2 years, 48.2 ± 5.0 kg/m^2 and 0.94 ± 0.07, respectively, while age and BMI at cancer diagnosis were 44.3 ± 8.1 years and 40.4 ± 6.7 kg/m^2, respectively. Patients received indicated surgical treatment: left quadrantectomy and axillary dissection with postoperative radiotherapy for infiltrating ductal breast carcinoma, ileal resection for carcinoid and total thyroidectomy and lymphadenectomy for papillary carcinoma.

Of the 43 "cancer" patients, 24 were morbidly obese at time of cancer diagnosis, 11 were obese (grade I or II), 7 were overweight and one was normal weight. All 43 had been morbidly obese at the time of their first bariatric visit.

Twenty-three morbidly obese patients (53.4%) received various bariatric operations: 12 laparoscopic adjustable gastric banding, 3 laparoscopic biliopancreatic diversion with duodenal-switch, 1 biliopancreatic diversion (Scopinaro), 1 laparoscopic gastric bypass, 1 vertical banded gastroplasty (Mason), and 5 BioEnterics intragastric balloon. In one patient, bariatric surgery was con-

Table 3. Site of malignancy in this obese population

site	N	Sex	Age (1)	BMI (2)	Diagnosed (3)
breast	9	F	44.2 ± 8.2	34.6 ± 8.4	8 pre/1 postop
thyroid	8	F	37.8 ± 6.7	40.1 ± 9.0	5 pre/2 work-up/1 postop
uterus	5	F	41.6 ± 7.2	38.9 ± 13.2	pre
ovary	3	F	34.6 ± 5.5	36.7 ± 6.5	pre
testicle	1	M	33	31	pre
GIST*	2	F	48.5 ± 16.2	43.3 ± 0.4	1 work-up/1 intraop
stomach	1	F	30	32	work-up
kidney	1	F	56	50	pre
skin melanoma	4	3F	37 ± 14.9	35.1 ± 7.9	pre
laryngeal	2	F/M	44.5 ± 12	36.1 ± 4.1	pre
hematol malignancies	3	2F	40 ± 7.0	37.5 ± 6.7	2 pre/1 work-up
others	4	F	52.7 ± 6.9	47 ± 11.1	3 work-up/1 postop

(1) Mean age at time of cancer diagnosis; (2) Mean BMI at cancer diagnosis; (3) Moment of cancer diagnosis reported to bariatric visit / bariatric operation: pre=before, intraop=intraoperative, post=postoperative.
*GIST = GI stromal tumor.

traindicated for anesthesiologic reasons (definitive tracheotomy after operation for laryngeal cancer).

Discussion

The results of this study showed that hormone-related tumors are the most prevalent in the morbidly obese population, consistent with previous reports.[8,18-21] No clear biologic mechanism has been proved showing the connection between obesity and non-endocrine component cancers.[21] Our obese subjects presenting malignant neoplasms were younger than normal weight subjects, previously reported.[22]

More than 62% of the patients presented hormone-related tumors, in agreement with larger epidemiological studies.[18,19] The most frequent for cancer in our obese patients was breast (20.1%). An inverse relationship between BMI and breast cancer in premenopausal[6,21,24,25] and a direct relationship between postmenopausal women[6] has been suggested. The increased serum concentration of bioavailable estradiol, from increased estrogen production by aromatase activity in excessive adipose tissue and from decreased serum concentration of sex-hormone-binding globulin, have been evoked as

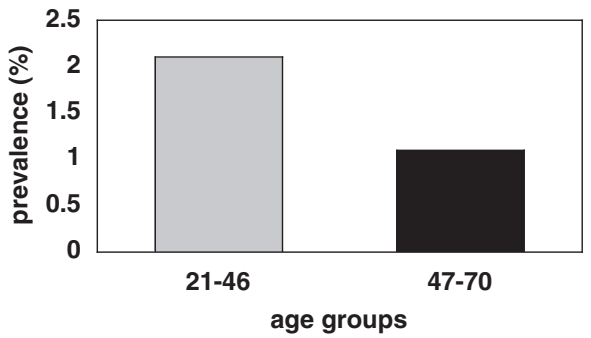

Figure 2. Prevalence of cancer by age groups in 1,333 obese patients.

Table 4. Treatment in 9 morbidly obese patients diagnosed with cancer/borderline tumors during preoperative work-up or intraoperatively

Tumor	Sex	BMI	Treatment
Warthin tumor	M	57.5	excision/Lap-BPD-DS
Gastric GIST	F	50	tumor excision/ Lap BPD-DS
Gastric GIST	F	43	tumor excision/ LAGB
Tongue carcinoma	F	54.4	tumor excision*
Thyroid	F	51.6	thyroidectomy*
Thyroid	F	53.4	thyroidectomy*
Early gastric cancer	F	33.1	total gastrectomy
Von Meyenburg disease†	F	43.3	laparoscopic diagnosis/biopsy
Multiple Myeloma	F	44	chemotherapy

Lap-BPD-DS=laparoscopic biliopancreatic diversion with duodenal switch; LAGB=laparoscopic adjustable gastric banding.
* Wait list bariatric surgery.
† Multiple bile duct hamartomas.[17]

potential mechanisms.[26-28] Thyroid cancer was the second most prevalent tumor (18.6%) in our database and all these patients were female. Obesity-related thyroid cancer has been previously described,[12,13,29,30] with a higher prevalence in men.[11] As in the breast cancer group, thyroid cancer occurred at a relatively young age (mean age 37.8 years).

Tumors of uterus, skin melanoma and gastric leiomyomas have been also found in our patients. Two patients were found to have asymptomatic gastric GIST (GI stromal tumors), reported as stromal tumor with borderline malignancy. One gastric carcinoma was discovered during the preoperative work-up; no bariatric surgery was indicated in this patient, who underwent total gastrectomy.

Although the prevalence of cancer in the Italian general population has been widely reported,[31-33] there has been no analysis from an Italian obese subjects database. Because different statistical methods were applied and there were larger cohorts of subjects in the general population studies, a comparison with our study would be considered with caution. The prevalence of cancer in our obese population was higher than the prevalence reported in the ITAPREVAL study of the general population from Southern Italy (1.3%) and similar to that in Northern Italy (3.6%).[31] However, the prevalence of malignant tumors among our obese subjects was higher than the average (2.7%) observed from all the areas covered by the Italian cancer registries.[31] That analysis showed also that the prevalence of all malignancies combined was 3.1% for females and 2.2% for males.[31] The majority of our obese subjects were females, so that their data are substantially in agreement with our finding (3.2%). Unlike the data from Italian cancer registries on the general population (obese and non-obese),[32,33] we found a higher prevalence of cancer in the younger obese group compared with the older one. This finding may suggest an independent role of obesity in increasing the prevalence of cancer among younger obese subjects. However, our observations need to be confirmed in a larger population of obese patients with malignant tumors.

In summary, this analysis found that morbidly obese patients from this Italian cohort have various tumors with a higher prevalence of hormone-related site-specific, female gender and younger age.

This study has limitations. First, it was retrospective, based on a database review, and no conclusion on risk of developing malignant neoplasm in obese subjects can be drawn. Second, the small number of patients with cancer did not permit calculation of the possible correlations among cancer and anthropometric and clinical variables. Nevertheless, this study may provide information on the prevalence of cancer in an obese Italian population. In fact, we believe that the homogeneous population characteristics, the fact that all patients were seen in a single academic bariatric institution, the availability of demographic measurements (weight, height, BMI, WHR, co-morbidities), and the multidisciplinary surveillance (bariatric surgeon, endocrinologist, nutritionist, psychiatrist), giving a very high likelihood of detection, could represent advantages of this database study. Furthermore, this report underlines that accurate work-up and rigorous follow-up for the more frequent malignancies should be beneficial in the management of morbidly obese patients.

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(Received April 6, 2005; accepted May 31,2005)