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Does Body Mass Index Influence the Onset and Prognosis of Colorectal Cancer?

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Abstract

Overweight and obesity are considered an increasing colorectal cancer risk factor. The association between excess body weight and colorectal cancer appears to be related to a state of systemic low-grade inflammation, due to an overproduction of proinflammatory cytokines.

The aim of this retrospective study was to verify the real clinical impact of body mass index (BMI) on the onset and prognosis of colorectal cancer. In this study, 419 patients submitted to surgery for colorectal cancer were divided in three classes of BMI. Patients with obesity represented 10.5% of the study population, and were significantly (p to verify the real clinical impact of body mass index (BMI) on the onset and prognosis of colorectal cancer. < 0.01) younger than patients without obesity. There were no differences in tumour stage, lymph node ratio (LNR) or carcinoembryonic antigen (CEA) levels between patients with obesity and patients without obesity. Disease-free survival and metastatic recurrence were worse in the obesity group compared to the normal weight group; however, this difference was not significant. These data suggest that BMI may contribute to earlier development of colorectal cancer due to a chronic inflammatory status.

Keywords: colorectal cancer; obesity; body mass index; chronic inflammation

Introduction

Obesity, defined as a body mass index (BMI) over 30 kg/m^2, is a global health issue that is increasing in both developing and developed countries[1, 2].

A systematic analysis showed that the global prevalence of overweight and obesity has risen by 27.5% for adults and 47.1% for children between 1980 and 2013 [1]. Similarly, according to another study, the prevalence of obesity has doubled in more than 70 countries between 1980 and 2015 [2]. This study quantified the burden of disease related to high BMI in 195 countries between 1990 and 2015, and revealed that excess body weight contributed to 4 million deaths and 120 million disability-adjusted life-years [2]. Indeed, overweight and obesity have been correlated with several medical conditions by epidemiological studies. In 2009, Guh et al. conducted a systematic review and meta-analysis to quantify the incidence of various co-morbidities related to obesity; the review found a statistically significant association between obesity and type II diabetes, cardiovascular diseases, and many types of cancer [3]. Pooled relative risks (RRs), obtained for 18 co-morbidities related to overweight and obesity, are reported in table 1 for males and females [3].

Table 1: Pooled relative risks with 95% confidence intervals (CIs), based on BMI, for each co-morbidity [3].

Comorbidity	Overweight		Obesity	
	Male	Female	Male	Female
Type II diabetes	2.40 [2.12–2.72]	3.92 [3.10–4.97]	6.74 [5.55–8.19]	12.41 [9.03–17.06]
Hypertension	1.28 [1.10–1.50]	1.65 [1.24–2.19]	1.84 [1.51–2.24]	2.42 [1.59–3.67]
Coronary Artery Disease	1.29 [1.18–1.41]	1.80 [1.64–1.98]	1.72 [1.51–1.96]	3.10 [2.81–3.43]
Congestive Heart Failure	1.31 [0.96–1.79]	1.27 [0.68–2.37]	1.79 [1.24–2.59]	1.78 [1.07–2.95]
Pulmonary Embolism	1.91 [1.39–2.64]	1.91 [1.39–2.64]	3.51 [2.61–4.73]	3.51 [2.61–4.73]
Stroke	1.23 [1.13–1.34]	1.15 [1.00–1.32]	1.51 [1.33–1.72]	1.49 [1.27–1.74
Breast Cancer	-	1.08 [1.03–1.14]	-	1.13 [1.05–1.22]
Colorectal Cancer	1.51 [1.37–1.67]	1.45 [1.30–1.62]	1.95 [1.59–2.39]	1.66 [1.52–1.81]
Endometrial Cancer	-	1.53 [1.45–1.61]	-	3.22 [2.91–3.56]
Oesophageal Cancer	1.13 [1.02–1.26]	1.15 [0.97–1.36]	1.21 [0.97–1.52]	1.20 [0.95–1.53]
Kidney Cancer	1.40 [1.31–1.49]	1.82 [1.68–1.98]	1.82 [1.61–2.05]	2.64 [2.39–2.90]
Ovarian Cancer	-	1.18 [1.12–1.23]	-	1.28 [1.20–1.36]
Pancreatic Cancer	1.28 [0.94–1.75]	1.24 [0.98–1.56]	2.29 [1.65–3.19]	1.60 [1.17–2.20]
Prostate Cancer	1.14 [1.00–1.31]	-	1.05 [0.85–1.30]	-
Asthma	1.20 [1.08–1.33]	1.25 [1.05–1.49]	1.43 [1.14–1.79]	1.78 [1.36–2.32]
Gallbladder Disease	1.09 [0.87–1.37]	1.44 [1.05–1.98]	1.43 [1.04–1.96]	2.32 [1.17–4.57]
Osteoarthritis	2.76 [2.05–3.70]	1.80 [1.75–1.85]	4.20 [2.76–6.41]	1.96 [1.88–2.04]
Chronic Back Pain	1.59 [1.34–1.89]	1.59 [1.34–1.89]	2.81 [2.27–3.48]	2.81 [2.27–3.48]

Bariatric surgery is the most effective treatment option to achieve successful long-term weight loss [4]. Compared with non-surgical treatment, bariatric surgery leads to greater weight reduction, greater remission rates of type 2 diabetes and more durable improvements in obesity-related co-morbidities [5, 6]. Furthermore, bariatric surgery has been associated with overall cancer risk reduction [7–9].

Colorectal cancer (CRC) is the third most diagnosed malignancy and the second leading cause of cancer-related deaths worldwide [10]. CRC aetiology and development are influenced by age, chronic disease history and other risk factors related to lifestyle, such as obesity, physical inactivity, unhealthy nutritional habits, smoking and alcohol consumption [11–14]. Several studies have revealed an association between obesity and an increased risk of colorectal cancer [15, 16]. A neoplastic mechanism that may be involved is the chronic inflammatory status that occurs in patients with obesity [17–22].

The aim of this study is to analyse, retrospectively, whether BMI influences the onset and prognosis of colorectal cancer.

Materials and Methods

Study Characteristics

The present work is retrospective study. Inclusion criteria were: (1) patients of all ages with positive preoperative histological diagnosis of CRC; (2) elective surgery performed between 2015 and 2018; (3) complete lymphadenectomy. Exclusion criteria were: (1) emergency surgery for tumor complications such as occlusion, perforation, and haemorrhage; (2) uncomplete lymphadenectomy; (3) post-operative complications of grade III or higher, measured according to the Clavien-Dindo classification [23].

Colorectal surgical procedures performed included right hemicolectomy, left hemicolectomy, anterior resection of the rectum, transverse colectomy, and total colectomy.

A complete lymphadenectomy was achieved in all patients included in the study. We considered a complete lymphadenectomy when the main mesenteric arteries and its branches were sectioned at the beginning, including in the resected specimen the mesocolon with its lymph nodes.

After surgery, patients completed a 3-year follow-up.

For each patient, the following data were collected: age, sex, BMI, tumour stage, lymph node ratio (LNR), preoperative carcinoembryonic antigen (CEA) levels, disease-free survival, mortality and metastasis.

Patients were classified into the following four BMI categories, defined according to World Health Organization (WHO) guidelines [24]: underweight (BMI < 19 kg/m2), normal weight (19 kg/m2 ≤ BMI ≤ 25 kg/m2), overweight (25 kg/m2 < BMI ≤ 30 kg/m2) and obese (BMI > 30 kg/m2). The underweight and normal weight classes were united into a single class, resulting in classification of the study population into three BMI categories.

Tumour stage was classified according to the TNM (tumor-node-metastasis) staging system and Astler-Coller modified Dukes staging system, as: Stage 0, Stage I, Stage II, Stage III and Stage IV (table 2).

Table 2: Correlation between tumour stage, TNM classification and Dukes classification (Astler-Coller modified).

Tumor stage	TNM classification			Dukes classification (Astler-Coller modified)
Stage 0	Tis	N0	M0	
Stage I	T1T2	N0N0	M0M0	AB1
Stage II	T3T4	N0N0	M0M0	B2B3
Stage III	Any TAny T	N1N2, N3	M0M0	C1(T2), C2(T3), C3(T4)C1(T2), C2(T3), C3(T4)
Stage IV	Any T	Any N	M1	D

Lymph node ratio (LNR) is defined as the number of positive lymph nodes divided by the total number of lymph nodes resected

and examined. Patients from the present study were divided according to LNR into three subgroups: class 1 when LNR was less than 0.05, class 2 when LNR was between 0.05 and 0.20, and class 3 when LNR was over 0.20.

Prior to colorectal surgery, blood samples were collected from patients to measure serum carcinoembryonic antigen (CEA) levels.

Statistics

Collected data were processed using SPSS statistical software.

Pearson's chi-squared test (χ^2) was conducted on categorical variables to compare frequencies. When data did not follow the normal distribution, the differences between groups were assessed using a non-parametric test and data were expressed as median and interquartile range (25^{th} and 75^{th} percentiles). Statistically significant differences were defined by $p < 0.05$.

Results

The retrospective study included 419 patients, of whom 336 had surgery for colon cancer and 83 had surgery for rectal cancer. Table 3 shows the type and rate of surgical procedures performed.

Table 3: Rate of surgical procedures performed

Surgical procedures (N=419)	N	%
Right hemicolectomy	168	40.1
Left hemicolectomy	156	37.2
Anterior resection of the rectum	83	19.8
Transverse colectomy	10	2.38
Total colectomy	2	0.47

Among the study's patients, there were 197 women (47%) and 222 men (53%), resulting in a male:female ratio of 1.13. The median age was 73 years, with a range of 65–79 (25^{th}–75^{th} percentile). The median value of BMI was 25, with a range of 23–28 (25^{th}–75^{th} percentile). Results of the classification according to BMI are shown in table 4.

Most of the study's population belonged to the normal weight and overweight classes. The underweight class (n = 19, 4.5%) and normal weight class (n = 197, 47.1%) were joined into a single class, showing a lower prevalence of the obesity class (n = 44, 10.5%) compared to the underweight/normal weight class (n = 216, 51.6%) and overweight class (n = 159, 37.9%).

Groups classified according to BMI presented different median ages: in the under-normal weight group, the median age was 74, in the overweight group it was 73, while in the obesity group it was 68.5. The difference between the median age of the BMI groups was statistically significant, with $p < 0.01$.

The proportions of males and females in the three different BMI groups is reported in table 4. In the under-normal weight group, there was a higher prevalence of females, while in the overweight group, males were the most represented; both differences were statistically significant, with $p < 0.05$. In the obesity group, the incidence of males and females was similar.

Table 4: Number and percentages of male and female patients in the under-normal weight, overweight and obesity groups.

*NS: non-significant.

		BMI class					
		Under-Normal weight		Overweight		Obesity	
		N	%	N	%	N	%
Gender	**Male (N=222)**	96	43.2	102	45.9	24	10.8
	Female (N=197)	120	60.9	57	28.9	20	10.2
			P<0.05		P<0.05		NS*

Tumour stage and LNR are shown in table 5. The most common tumour stages were stage II and stage III. The most represented LNR class was class I, with an LNR less than 0.05. The total number of lymph nodes resected in the study's population was 5723 on 419 patients (mean: 13.6).

Table 5: Number and percentages of patients in each tumour stage and lymph node ratio class.

*Data collected for 408 patients.

		N	%
Tumor stage	0	27	6.4
	I	76	18.1
	II	150	35.8
	III	150	35.8
	IV	16	3.8
Lymph node ratio*	<0.05	272	66.7
	0.050.20	82	20.1

Incidence of the different tumour stages was analysed in the under-normal weight, overweight and obesity groups, as shown in table 6. The results did not reveal a statistically significant correlation between tumour stage and BMI.

Table 6: Number and percentages of patients in the under-normal weight, overweight and obesity groups for each tumour stage.

*NS: non-significant.

		Under-normal weight		Overweight		Obesity	
		N	**%**	**N**	**%**	**N**	**%**
Tumor stage	0	13	48.1	11	40.7	3	11.1
	I	34	44.7	35	46.1	7	9.2
	II	78	52.0	56	37.3	16	10.7
	III	82	54.7	51	34.0	17	11.3
	IV	9	56.2	6	37.5	1	6.2
			NS*		**NS**		**NS**

Prevalence of the three LNR classes was compared among BMI groups, as reported in table 7. The association between LNR and BMI was not statistically significant.

Table 7: Number and percentages of patients in the under-normal weight, overweight and obesity groups in each lymph node ratio class.

*NS: non-significant.

		Under-normal weight		Overweight		Obesity	
		N	**%**	**N**	**%**	**N**	**%**
Lymph node ratio	<0.05	134	49.3	110	40.4	28	10.3
	0.05-0.20	32	59.3	16	29.6	6	11.1
	>0.20	47	57.3	25	30.5	10	12.2
			NS*		**NS**		**NS**

Preoperative serum CEA levels were examined in 193 patients and the median value was 3.9, with a range of 2.0–10.3 (25^{th}–75^{th} percentile). The median value of CEA was compared between the under-normal weight group, overweight group and obesity group. The association between CEA and BMI was not statistically significant, as shown in table 8.

Table 8: Median and 25^{th}–75^{th} percentile range of CEA values in the three BMI classes.

*NS: non-significant.

	Under-normal weight		**Overweight**		**Obesity**		
	Median	25^{th}P – 75^{th}P	Median	25^{th}P – 75^{th}P	Median	25^{th}P – 75^{th}P	
CEA	4.0	2.0-10.5	4.03	1.9-11.5	3.14	1.8-5	**NS***

In accordance with inclusion and exclusion criteria, the surgical complications that occurred in the study population were only of grade I and II. In the under-normal weight group 10% of patients developed urinary tract infection (UTI), 10% wound infection (WI) and 6% pulmonary infection (PI); the same complications occurred in the overweight group (UTI: 18%; WI: 18%; PI: 12%) and in the obesity group (UTI: 13%; WI: 18%; PI: 20%)

The median disease-free survival (DFS), calculated using Kaplan-Meier analysis, was 84 months, with a 5% estimated error (figure 1).

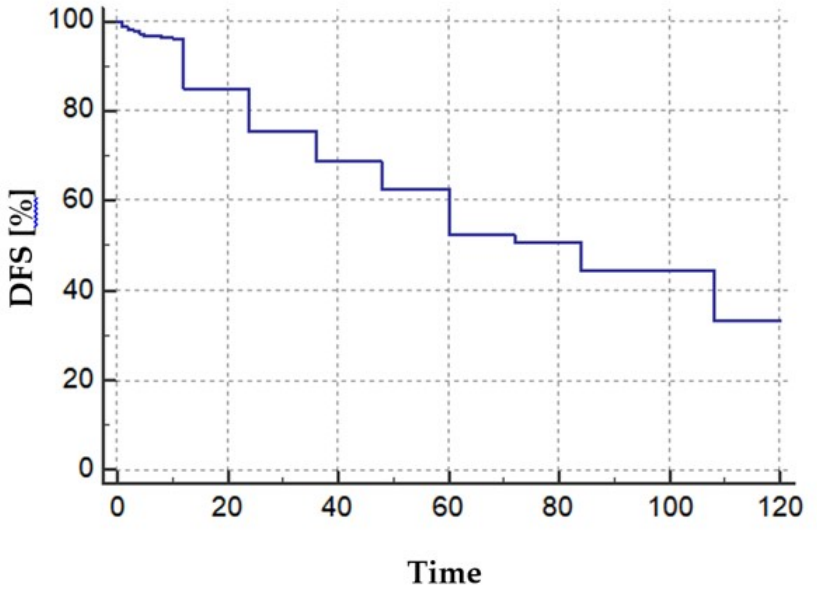

Figure 1: Kaplan-Meier curve showing disease-free survival

The Kaplan-Meier method was used to compare the probability of survival among BMI classes, as reported in figure 2. Prognosis, analysed in relation to BMI, DFS and metastatic recurrence, was better for the under-normal weight group compared to the obese group, but this difference was not statistically significant.

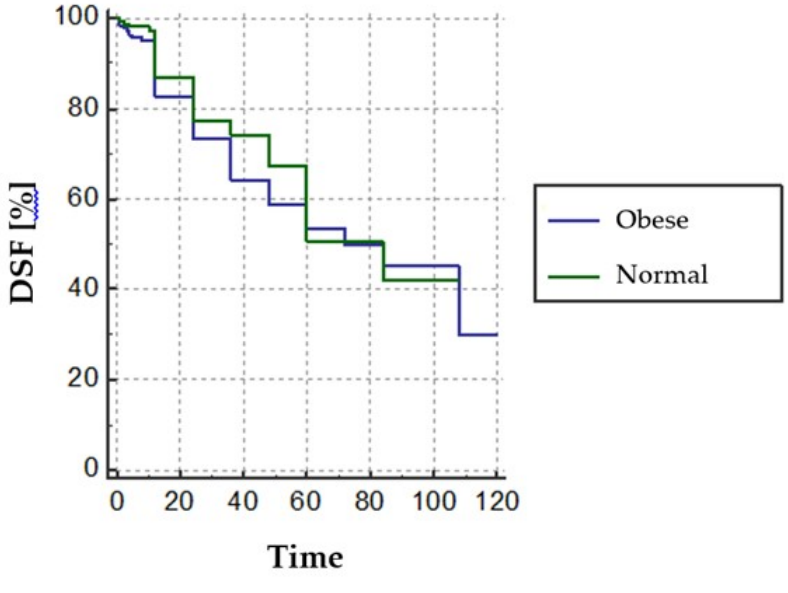

Figure 2: Disease-free survival according to body mass index class, showing a better, but not significant, outcome in normal and underweight patients

Discussion

The relationship between obesity and colorectal cancer has been investigated in recent years in a large number of studies and papers. Obesity can be evaluated through different solid anthropometric indexes, such as BMI, waist circumference (WC) and waist--to-hip ratio (WHR); the first reflects overall obesity, whereas WC and WHR are commonly used to measure abdominal obesity [25]. In 2007, a meta-analysis of 15 cohort studies showed that obesity is a statistically significant risk factor for colorectal cancer; the pooled relative risk of CRC, measured by BMI, was 1.37 for men with overweight and obesity and 1.07 for women, demonstrating a more significant correlation in men than in women [26].

In 2013, Ma et al. conducted a systematic review and meta-analysis to assess the association between both general and central obesity and colorectal cancer risk. The review included 41 prospective studies on general obesity and 13 studies on abdominal obesity, published between 1992 and 2012, and found that higher BMI and greater WC lead to an increased equal risk for colon and rectal cancer [15].

The role of abdominal obesity in CRC development was further investigated in 2017 by Dong et al., who conducted a meta-analysis of 19 prospective cohort studies. The results indicated a significant association between greater WC and WHR and an increased risk of total colorectal cancer, colon cancer and rectal cancer [16].

In 2019, Soltani et al. examined the correlation between diagnosis of CRC, obesity and diabetes in a case control study, which included 693 participants who had a colonoscopy between 2015 and 2017 [27]. The case group (n = 178) included patients who had a diagnosis of CRC determined by colonoscopy, while the control group (n = 515) included individuals with a colonoscopy negative for polyps and CRC. The study revealed a significant association between obesity and CRC diagnosis: the incidence of overweight/obesity was higher in the case group than in the control group (49.9% and 0.9%, respectively). Furthermore, in the group of patients with a diagnosis of CRC, there was a higher incidence of positive history of diabetes compared to the group with a normal

colonoscopy (19.1% and 10.9%, respectively) [27].

In our retrospective analysis, among the study population affected by CRC, a smaller proportion were members of the obesity group compared to the under-normal weight and overweight classes. However, patients with obesity were significantly younger than under-normal weight patients, revealing an association between age and BMI. Despite the younger age of diagnosis in patients with obesity, these patients did not show a more advanced stage of cancer. Indeed, our study did not reveal a statistically significant association between tumour stage and BMI.

LNR is considered an important prognostic factor in colorectal cancer [28–31]; high values of LNR are correlated with lower overall survival (OS) and worse disease-free survival (DFS) [28]. Preoperative serum CEA is an independent prognostic factor for colorectal cancer; elevated concentrations of CEA before surgery are associated with impaired oncological outcomes, including increased overall mortality, and decreased overall and disease-free survival [32, 33]. However, there were no statistically significant differences in LNR values and CEA levels between patients with and without obesity. In addition, disease-free survival and metastatic recurrence were better for the under-normal weight group compared to the obesity group; however, this difference was not statistically significant.

In conclusion, these data reflect how obesity may induce faster tumour progression and earlier onset of symptomatic CRC, as patients with obesity affected by CRC were younger than under-normal weight patients.

The link between obesity and CRC might be the accumulation of visceral adipose tissue (VAT), which is associated, through various mechanisms, with systemic low-grade inflammation, a favourable niche for tumour development [17]. Involvement of VAT in inflammatory processes has been suggested by the direct finding that adipose tissue is infiltrated by significant numbers of macrophages [17, 18]. Both macrophages, infiltrated in visceral fat, and adipocytes are responsible for producing and secreting proinflammatory cytokines/adipokines such as interleukin-6 and tumour necrosis factor-α [17, 19, 20]. Macrophage infiltration in adipose tissue and the production of proinflammatory mediators and growth factors have profound consequences on the local microenvironment; these effects include promotion of cellular proliferation, reduction of apoptosis, stimulation of epithelial-mesenchymal transition, cell migration and angiogenesis. Through these mechanisms, the chronic inflammation associated with VAT promotes tumour initiation, growth, progression and metastasis [21, 22].

The effect of bariatric surgery on colorectal cancer risk is uncertain and controversial [34–36]. A recent metanalysis showed that patients who underwent bariatric surgery exhibited a greater than 35% reduction in the risk of developing CRC compared with patients with obesity that had no surgery [37]. Similarly, a cohort study revealed that patients who had bariatric surgery had a decreased risk of developing hormone-related cancers (like breast, endometrium and prostate cancer) compared to the no-surgery group [36]. Regarding the type of bariatric surgery, gastric bypass resulted in the largest risk reduction for hormone-related cancers (OR 0.16, 0.11 to 0.24), but it was associated with an increased risk of CRC (OR 2.63, 1.17 to 5.95). This increased risk was not associated with gastric banding or sleeve gastrectomy [36].

Conclusions and Future Perspectives

In conclusion, our retrospective analysis of CRC patients revealed a significantly lower median age of the patients with obesity as compared to the under-normal weight patients. This finding highlights that BMI may contribute to early onset and development of CRC, but it is not related to a worse prognosis as BMI is not associated with LNR, DFS and metastatic recurrences. The earlier neoplastic onset in obese patients may be related to a state of chronic inflammation related to obesity.

Patients submitted to bariatric surgery constitute a young population at risk for obesity-related co-morbidities, including CRC. Further studies are required, both to clarify the controversial association between bariatric surgery and CRC, and to confirm the influence of BMI on CRC onset and prognosis.

Statements and Declarations

Ethics Approval and Consent to Participate: The need for the study approval was waived by the Catania 2 Ethics Committee due to the retrospective, observational and anonymous nature of the study. All methods were carried out in accordance with relevant guidelines and regulations.

Informed consent was obtained from all subjects involved in the study.

Consent for Publication

Not applicable

Availability of Data and Materials

The datasets generated and analyzed during the current study are not publicly available due to the possibility of patients' identification and restriction of Morgagni Foundation in sharing patients' data, but are available from the corresponding author on reasonable request.

Competing Interests

The authors declare no conflict of interest.

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Author Contributions

Conceptualization: Stefano Puleo and Saverio Latteri; Methodology: Maria Sofia; Validation: Sergio Castorina, Stefano Puleo and Saverio Latteri; Formal analysis, Filippo Palermo; Investigation, Ornella Coco; Resources: Sergio Castorina and Stefano Puleo; Data curation: Filippo Palermo and Ornella Coco; Writing—original draft preparation: Sara D'Amato and Maria Sofia; Writing—review and editing: Maria Sofia and Stefano Puleo; Supervision: Stefano Puleo. All authors have read and agreed to the published version of the manuscript.

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