Colorectal Cancer Prognosis Following Obesity Surgery in a Population-Based Cohort Study

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters

Citation
Tao, Wenjing, Peter Konings, Mark A. Hull, Hans-Olov Adami, Fredrik Mattsson, and Jesper Lagergren. 2016. “Colorectal Cancer Prognosis Following Obesity Surgery in a Population-Based Cohort Study.” Obesity Surgery 27 (5): 1233-1239. doi:10.1007/s11695-016-2431-6. http://dx.doi.org/10.1007/s11695-016-2431-6.

Published Version
doi:10.1007/s11695-016-2431-6

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:33029946

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Colorectal Cancer Prognosis Following Obesity Surgery in a Population-Based Cohort Study

Wenjing Tao1 · Peter Konings1 · Mark A. Hull2 · Hans-Olov Adami3,4 · Fredrik Mattsson1 · Jesper Lagergren1,5

Published online: 7 November 2016
© The Author(s) 2016. This article is published with open access at Springerlink.com

Abstract
Background Obesity surgery involves mechanical and physiological changes of the gastrointestinal tract that might promote colorectal cancer progression. Thus, we hypothesised that obesity surgery is associated with poorer prognosis in patients with colorectal cancer.
Methods This nationwide population-based cohort study included all patients with an obesity diagnosis who subsequently developed colorectal cancer in Sweden from 1980 to 2012. The exposure was obesity surgery, and the main and secondary outcomes were disease-specific mortality and all-cause mortality, respectively. Cox proportional hazard survival models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs), adjusted for sex, age, calendar year and education level.
Results The exposed and unexposed cohort included 131 obesity surgery and 1332 non-obesity surgery patients with colorectal cancer. There was a statistically significant increased rate of colorectal cancer deaths following obesity surgery (disease-specific HR 1.50, 95% CI 1.00–2.19). When analysed separately, the mortality rate was more than threefold increased in rectal cancer patients with prior obesity surgery (disease-specific HR 3.70, 95% CI 2.00–6.90), while no increased mortality rate was found in colon cancer patients (disease-specific HR 1.10, 85% CI 0.67–1.70).
Conclusion This population-based study among obese individuals found a poorer prognosis in colorectal cancer following obesity surgery, which was primarily driven by the higher mortality rate in rectal cancer.

Keywords Bariatric surgery · Colorectal neoplasms · Mortality · Survival · Registry

Introduction
Obesity is associated with increased incidence and decreased survival in several malignancies, including colorectal cancer [1, 2]. Some studies have also shown an overall
indicate more aggressive tumour growth [11]. The aim of this study was to elucidate the association between obesity surgery and colorectal cancer prognosis, and we hypothesised that obesity surgery worsens the prognosis for patients with colorectal tumours.

Methods

Study Design

This was a nationwide, population-based cohort study including all patients with a hospital discharge diagnosis of obesity in the Swedish Patient Registry combined with a diagnosis of colorectal cancer in the Swedish Cancer Registry from 1st of January 1980 to 31st of December 2012. The Swedish Patient Registry holds information on hospital discharges in Sweden, including admission and discharge dates, main- and co-diagnoses and surgical procedures. This register was 85% nationally complete between 1980 and 1986 and has been 100% complete since 1987 [12]. The registration of surgical procedure codes in the Patient Registry is >95% accurate and >98% complete [13]. The Cancer Registry records cancer cases in Sweden since 1958; it has an overall completeness of 98%, and 99% of the tumours are morphologically verified [14]. The registries can be linked by means of the unique 10-digit personal identity numbers assigned to all Swedish residents upon birth or immigration [15]. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (reference number 2012/210-31/2). No informed consent from participants is required for register-based studies according to Swedish law.

Follow-Up

The main study outcome was colorectal cancer-specific survival, measured through disease-specific deaths, and the secondary outcome was overall survival, measured through all-cause deaths. Dates and causes of death were ascertained through record linkage based on the personal identity numbers from the Swedish Causes of Death Registry. Colorectal cancer-specific deaths were identified through the diagnosis codes 153-154 in ICD7 (corresponding to C18-C20 in ICDO3) in the Cancer Registry. Only patients with colorectal cancer as their first cancer and who received this diagnosis after the date of obesity diagnosis or date of obesity surgery were included in the study. The cohort of obese study participants was grouped into those who had undergone obesity surgery (exposed) and those who had not (unexposed). Obesity surgery was ascertained from surgical codes in the Patient Register: 4750-4754 before 1997, and JFD00-01, JDF10-11, JDF20-21 and JFD00 from 1997 and onwards according to the NOMESCO Classification of Surgical Procedures.

Statistical Analysis

Cox proportional hazard models were used to calculate hazard ratio (HR) with 95% confidence intervals (CI) for disease-specific and all-cause mortality, comparing obese cohort members with and without a history of obesity surgery prior to their colorectal cancer diagnosis. The analyses were performed for colon and rectal cancer patients combined as well as separately. Time to event was defined as the time elapsed from the date of colorectal cancer diagnosis until the first occurrence of any of the following: death, metastatic disease, or local recurrence.
events: death, emigration or end of follow-up (December 31, 2012). In multivariate modelling, HRs were adjusted for the following potential confounders: sex, age at diagnosis (continuous), calendar period (categorised into 1980–1999 and 2000–2012) and education level (categorised into low [≤9 years], medium [10–12 years] and high [≥12 years] based on the Swedish schooling system). We included an interaction term between surgery and tumour location (colon or rectum) to assess differences in HR between tumour sites and evaluated significance with the likelihood ratio test. Model assumptions and fit were assessed formally and graphically. A penalized spline for age was introduced in the colon cancer subgroup analysis in order to satisfy the proportional hazard assumption [18]; smoothing parameters were selected based on the Akaike information criterion [19]. In a separate analysis, we modelled obesity surgery as a categorical variable with four possible values (no surgery, gastric bypass, restrictive procedures [gastric banding and vertical banded gastroplasty] and malabsorptive procedures) to evaluate whether the type of obesity procedure affects colorectal cancer prognosis differently.

Because information on education level was missing for 4% of the patients, we used multiple imputations by chained equations under a missing at random assumption for this variable in the multivariate model [20]. Sensitivity analysis with a complete-case analysis under the missing completely at random assumption, and multiple imputations under the missing-not-at-random assumption yielded similar results [21]. All statistical tests were two-sided, and results were considered significant at a 5% significance level. The statistical software R was used for all statistical analyses [22].

Results

Study Participants

The study cohort consisted of 1463 patients with an obesity diagnosis followed by a colorectal cancer diagnosis during the study period. Among these patients, 1009 had colon cancer (69%), 449 had rectal cancer (31%) and 5 had both colon and rectal cancer codes. Altogether, 131 (9%) had undergone obesity surgery, while the remaining
1332 patients had not. A flowchart describing the inclusion and exclusion of patients is presented in Fig. 1. Characteristics of the obesity surgery and non-obesity surgery cohort members are presented in Table 1. The obesity surgery group was younger and included more women than the non-obesity surgery group, while diabetes and cardiovascular diseases were more common in non-obesity surgery patients.

Out of 45 (34%) patients in the obesity surgery cohort that died during the study period, 32 (24%) died from colorectal cancer. The number of deaths among the non-obesity surgery cohort members was 596 (45%), of whom 354 (27%) died from colorectal cancer. The median length of follow-up was 3.7 years among obesity surgery and 4.3 years among non-obesity surgery participants. The survival proportions are presented in Fig. 2. Most patients

| Table 1 Characteristics of patients with a diagnosis of colorectal cancer and obesity, who had or had not undergone obesity surgery, between 1980 and 2012 in Sweden |
|-----------------------------------------------|
| **Age at colorectal cancer diagnosis, years** | **No obesity surgery** | **Obesity surgery** |
|                                               | \((n = 1332)\)         | \((n = 131)\)       |
| Number (%)                                    |                       |
| <56                                           | 240 (18)              | 62 (47)              |
| ≥56                                           | 1092 (82)             | 69 (53)              |
| **Sex**                                       |                       |
| Male                                          | 679 (51)              | 40 (31)              |
| Female                                        | 653 (49)              | 91 (69)              |
| **Year of colorectal cancer diagnosis**       |                       |
| 1980–1999                                     | 413 (31)              | 30 (23)              |
| 2000–2012                                     | 919 (69)              | 101 (77)             |
| **Obesity surgery procedure**                 |                       |
| Gastric bypass                                | –                     | 34 (26)a             |
| Gastric banding                               | –                     | 43 (33)a             |
| Vertical banded gastroplasty                  | –                     | 47 (36)a             |
| Malabsorptive surgery                         | –                     | 7 (5)a               |
| **Education**                                 |                       |
| Low (≤9 years)                                | 634 (48)              | 46 (35)              |
| Medium (10–12 years)                          | 460 (35)              | 61 (47)              |
| High (>12 years)                              | 183 (14)              | 18 (14)              |
| Missing                                       | 55 (4)                | 6 (5)                |
| **Comorbidity**                               |                       |
| Diabetes                                      | 427 (32)              | 29 (22)              |
| Cardiovascular disease                        | 289 (22)              | 13 (10)              |
| Hypertension                                  | 481 (36)              | 39 (30)              |
| Chronic obstructive pulmonary disease         | 120 (9)               | 8 (6)                |
| **Colorectal cancer**                         |                       |
| \(1332^b\)                                    | 131^b                 |
| Colon cancer                                  | 917 (69)              | 97 (74)              |
| Rectal cancer                                 | 419 (31)              | 35 (26)              |
| **Tumour stage (TNM)**                        |                       |
| 0–I                                           | 192 (14)              | 16 (12)              |
| II–III                                        | 304 (23)              | 32 (24)              |
| IV                                            | 107 (8)               | 19 (15)              |
| Unknown                                       | 729 (55)              | 64 (49)              |

\[a\] One patient in the obesity surgery cohort was coded with gastric bypass and non-gastric bypass surgery simultaneously.  
\[b\] One patient in the obesity surgery cohort and four patients in the non-obesity surgery cohort were diagnosed with colon and rectal cancer simultaneously.  
\[c\] Patients for whom data on tumour stage were available. Data on tumour stage were only available in patients diagnosed from 2004 and onward.
with colorectal cancer as the cause of death died within the first 5 years of diagnosis.

**Colorectal Cancer Survival**

Colorectal cancer patients who had undergone prior obesity surgery experienced higher cancer-specific (HR 1.50; 95% CI 1.00–2.19) and overall mortality rates (HR 1.62; 95% CI 1.18 to 2.22) than patients without such surgery (Table 2). Separate analyses of colon and rectal cancer patients revealed no significant difference in mortality rates between obesity surgery and non-obesity surgery patients with respect to colon cancer (disease-specific HR 1.10; 95% CI 0.67–1.70). However, cancer-specific deaths in rectal cancer patients were threefold higher in those who had undergone previous obesity surgery compared to those who had not (disease-specific HR 3.70; 95% CI 2.00–6.90). Overall survival mirrored the disease-specific survival (Table 2). In a separate analysis, obesity surgery was categorized according to type of procedure. The results showed borderline significant association between colorectal cancer-specific mortality and restrictive procedures (HR 1.49; 95% CI 1.00–2.22) and no significant association with gastric bypass or malabsorptive procedures.

**Discussion**

This study indicates that among obese individuals diagnosed with colorectal cancer, previous obesity surgery had a negative prognostic impact on cancer survival that was primarily driven by the threefold higher rates of cancer deaths in patients with rectal cancer.

Colorectal cancer is the only known malignancy where the risk of being diagnosed with the disease seems to increase after obesity surgery [7, 8]. The present study suggests that this increase translates into poorer survival in rectal cancer but not colon cancer when compared to obese controls. Differences in aetiology and biological mechanisms between colon and rectal cancer might explain the divergent findings between the tumour sites [23]. The somatic mutation profile is similar between colon and rectal tumours, but there are differences in phenotype and effect modifiers [24–26]; it is, e.g. recognised that obesity is a stronger risk factor for colon cancer than rectal cancer [2, 27, 28]. Furthermore, colon and rectal cancers face different treatment regimens. Preoperative radiotherapy is for example used in rectal cancer but not in colon cancer. We cannot exclude that other

**Table 2** Obesity surgery and all-cause or disease-specific death among obese patients with colorectal cancer, presented as hazard ratio (HR) and 95% confidence interval (CI)

| Mortality           | No. of patients, surgery | No. of patients, no surgery | Unadjusted HR | 95% CI     | P value | Adjusted HRa | 95% CI     | P value |
|---------------------|--------------------------|-----------------------------|---------------|------------|---------|--------------|------------|---------|
| Colorectal cancer   |                          |                             |               |            |         |              |            |         |
| Disease-specific deaths | 32                        | 354                         | 1.09          | 0.76 to 1.6 | 0.64    | 1.50         | 1.00 to 2.19 | 0.04    |
| All deaths          | 45                        | 596                         | 1.30          | 0.96 to 1.8 | 0.09    | 1.62         | 1.18 to 2.22 | <0.001  |
| Colon cancer        |                          |                             |               |            |         |              |            |         |
| Disease-specific deaths | 20b                      | 251                         | 0.71          | 0.45 to 1.10 | 0.14    | 1.10         | 0.67 to 1.70 | 0.75    |
| All deaths          | 29                        | 419b                        | 0.60          | 0.41 to 0.87 | 0.0078  | 1.28         | 0.87 to 1.90 | 0.21    |
| Rectal cancer       |                          |                             |               |            |         |              |            |         |
| Disease-specific deaths | 13b                      | 103                         | 1.80          | 1.00 to 3.30 | 0.038   | 3.70         | 2.00 to 6.90 | <0.0001 |
| All deaths          | 16                        | 177b                        | 1.60          | 0.97 to 2.60 | 0.064   | 3.00         | 1.80 to 5.10 | <0.0001 |

a Adjusted for sex, age at diagnosis, year of diagnosis, and education. Missing data on education (4%) was imputed under the missing-at-random assumption

b One patient in the obesity surgery cohort was diagnosed with both colon and rectal cancer simultaneously and died of rectal cancer; four patients in the non-obesity surgery cohort were diagnosed with both colon and rectal cancer simultaneously, and two patients died of other causes than colorectal cancer.
confounding factors, e.g. changes in lifestyle factors, may have contributed to the worse prognosis in rectal cancer following bariatric surgery. However, any such confounding should be similar for colon cancer. Moreover, it is likely that lifestyle habits changed to more healthy behaviours and increased health awareness following obesity surgery.

A study of patients undergoing gastric bypass for obesity found hyperproliferation of the rectal mucosa as a result of increased expression of proinflammatory genes from 6 months up to 3 years after surgery [11], indicating potentially more aggressive tumour growth. Our study could, however, not confirm if type of bariatric procedure had an impact on colorectal cancer prognosis. Most of the patients in the cohort had undergone restrictive obesity surgery (69%), and the sample size was not sufficiently powered to evaluate the association between specific types of bariatric procedure and colorectal cancer-specific deaths.

The overall higher rate of deaths observed in obesity surgery patients in this study contradicts previous findings that obesity surgery is protective of mortality. However, our analyses are limited to patients with colorectal cancer, and a majority of these patients succumbed to their cancer (71%). Thus, findings from the all-cause mortality analysis were mainly influenced by disease-specific mortality.

Strengths of this study include the population-based cohort design including all patients with colorectal cancer and obesity diagnosis from nationwide Swedish registers that reduces selection bias and increases generalisability of the results. The high validity of the registers from which data on study exposure and outcomes were obtained decreases the risk of information bias. However, a limitation is that only patients with a recorded diagnosis of obesity were included, which possibly excludes obese patients who are otherwise healthy. The results were adjusted for several confounding factors, but we lacked information on other potential confounders including body mass index. As there have been large changes in treatment options during the long study period, we adjusted for calendar period to account for this variation. Tumour stage is commonly adjusted for in cancer survival studies; however, as obesity surgery might lead to altered pathophysiology, tumour stage could be a mediator in the causal pathway between obesity surgery and colorectal cancer prognosis and were thus not adjusted for in this study. We searched for colorectal cancer deaths in both underlying and contributing causes of death. Whether this inclusion overestimates the number of colorectal cancer deaths is unknown, but there is no reason to believe that any such misclassification would be differential between obesity surgery patients and obese controls. Non-differential misclassification of outcome would only dilute associations, and thus not explain the increased mortality in rectal cancer [29]. Finally, we cannot exclude that the findings in the present study are due to chance, in spite of the strong and statistically significant association between obesity surgery and rectal cancer.

In conclusion, this nationwide, Swedish cohort study with long and complete follow-up found increased mortality from rectal cancer, but not from colon cancer, following obesity surgery. Since this is the first study addressing this question, more research is needed before a definite association can be concluded. If the association is true, clinicians should be made aware of the increased risk and poorer prognosis of rectal cancer in patients with prior obesity surgery.

Compliance with Ethical Standards

Funding This study was funded by the Swedish Research Council SIMSAM (D0547801), the Nordic Cancer Union (154860), the Swedish Cancer Society (140322) and Karolinska Institutet Distinguished Professor Award to Prof. Hans-Olov Adami (2368/10-221).

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Regional Ethical Review Board in Stockholm (DNR 2012/210-31/2).

Informed Consent For this type of study, formal consent is not required.

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

Contributors All authors contributed to the study concept, design and interpretation of data. Author 1 developed the research aim, collected the data, and drafted the manuscript. Author 2 conducted the statistical analysis. The final manuscript was revised and approved by all authors.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. Gut. 2013;62(6):933–47.
2. Campbell PT, Newton CC, Dehal AN, et al. Impact of body mass index on survival after colorectal cancer diagnosis: the cancer prevention study-II nutrition cohort. J Clin Oncol. 2012;30(1):42–52.
3. Sjostrom L, Gummesson A, Sjostrom CD, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish obese subjects study): a prospective, controlled intervention trial. Lancet Oncol. 2009;10(7):653–62.
4. Adams TD, Stroup AM, Gress RE, et al. Cancer incidence and mortality after gastric bypass surgery. Obesity (Silver Spring). 2009;17(4):796–802.
5. Christou NV, Lieberman M, Sampalis F, et al. Bariatric surgery reduces cancer risk in morbidly obese patients. Surg Obes Relat Dis. 2008;4(6):691–5.

6. McCawley GM, Ferriss JS, Geffel D, et al. Cancer in obese women: potential protective impact of bariatric surgery. J Am Coll Surg. 2009;208(6):1093–8.

7. Derogar M, Hull MA, Kant P, et al. Increased risk of colorectal cancer after obesity surgery. Ann Surg. 2013;258(6):983–8.

8. Ostlund MP, Lu Y, Lagergren J. Risk of obesity-related cancer after obesity surgery in a population-based cohort study. Ann Surg. 2010;252(6):972–6.

9. Tao W, Lagergren J. Clinical management of obese patients with cancer. Nat Rev Clin Oncol. 2013;10(9):519–33.

10. Quercia I, Dutia R, Kotler DP, et al. Gastrointestinal changes after bariatric surgery. Diabetes Metab. 2014;40(2):87–94.

11. Kant P, Sainsbury A, Reed KR, et al. Rectal epithelial cell mitosis and expression of macrophage migration inhibitory factor are increased 3 years after Roux-en-Y gastric bypass (RYGB) for morbid obesity: implications for long-term neoplastic risk following RYGB. Gut. 2011;60(7):893–901.

12. Ludvigsson JF, Andersson E, Ekborn A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

13. Nilsson AC, Spetz CL, Carsjo K, et al. Reliability of the hospital registry. The diagnostic data are better than their reputation. Lakartidningen. 1994;91(7):598. 603-5

14. Barlow L, Westergen K, Holmberg L, et al. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009;48(1):27–33.

15. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659–67.

16. National Board of Health and Welfare. Dödsorsaksstatistik: Historik, produktionsmetoder och tillförlighet. Stockholm: Socialstyrelsen; 2010 .https://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18019/2010-4-33.pdf. Accessed 24 Sept 2016

17. Statistics Sweden. Historic Population Register. Örebro: SCB; 2006 .http://www.scb.se/statistik/_publikationer/BE9999_2006A01_BR_BE96ST0603.pdf. Accessed 24 Sept 2016

18. Eilers PH, Marx BD. Flexible smoothing with B-splines and penalties. Stat Sci. 1996;11:89–121.

19. Hurvich CM, Simonoff JS, Tsai C. Smoothing parameter selection in nonparametric regression using an improved Akaike information criterion. JRSSB. 1998;60:271–93.

20. Van Baaren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. J Stat Softw. 2011;45(3):1–67.

21. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York: Springer; 2000.

22. R: A language and environment for statistical computing. R Foundation for Statistical Computing [computer program]. Version 3.1.2. Vienna: R Core Team; 2015. Available at: http://www.R-project.org/.

23. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487(7407):330–7.

24. Slattery ML, Curtin K, Wolff RK, et al. A comparison of colon and rectal somatic DNA alterations. Dis Colon rectum. 2009;52(7):1304–11.

25. Frattini M, Balestra D, Suardi S, et al. Different genetic features associated with colon and rectal carcinogenesis. Clin Cancer Res. 2004;10(12 Pt 1):4015–21.

26. Einspahr JG, Krouse RS, Yoshim JM, et al. Association between cyclooxygenase expression and colorectal adenoma characteristics. Cancer Res. 2003;63(14):3891–3.

27. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. Am J Clin Nutr. 2007;86(3): 556–65.

28. Ma Y, Yang Y, Wang F, et al. Obesity and risk of colorectal cancer: a systematic review of prospective studies. PLoS One. 2013;8(1): e53916.

29. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. 3 ed. Philadelphia: Lippincott Williams & Wilkins; 2008.