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Increased Risk of Colorectal Cancer After Obesity Surgery

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Objective: The purpose was to determine whether obesity surgery is associated with a long-term increased risk of colorectal cancer.

Background: Long-term cancer risk after obesity surgery is not well characterized. Preliminary epidemiological observations and human tissue biomarker studies recently suggested an increased risk of colorectal cancer after obesity surgery.

Methods: A nationwide retrospective register-based cohort study in Sweden was conducted in 1980–2009. The long-term risk of colorectal cancer in patients who underwent obesity surgery, and in an obese no surgery cohort, was compared with that of the age-, sex- and calendar year-matched general background population between 1980 and 2009. Obese individuals were stratified into an obesity surgery cohort and an obese no surgery cohort. The standardized incidence ratio (SIR), with 95% confidence interval (CI), was calculated.

Results: Of 77,111 obese patients, 15,095 constituted the obesity surgery cohort and 62,016 constituted the obese no surgery cohort. In the obesity surgery cohort, we observed 70 patients with colorectal cancer, rendering an overall SIR of 1.60 (95% CI 1.25–2.02). The SIR for colorectal cancer increased with length of time after surgery, with a SIR of 2.00 (95% CI 1.48–2.64) after 10 years or more. In contrast, the overall SIR in the obese no surgery cohort (containing 373 colorectal cancers) was 1.26 (95% CI 1.14–1.40) and remained stable with increasing follow-up time.

Conclusions: Obesity surgery seems to be associated with an increased risk of colorectal cancer over time. These findings would prompt evaluation of colonoscopy surveillance for the increasingly large population who undergo obesity surgery.

Keywords: Bariatric surgery, cancer, gastrointestinal, neoplasm, weight loss

Obesity [defined as a body mass index (BMI) > 30 kg/m²] is one of the major global health problems of the 21st century. Since 1980, the prevalence of obesity has nearly doubled, and currently more than half a billion of the global adult population can be classified as obese. Correspondingly, the incidence of obesity surgery has increased dramatically during the past 3 decades. The number of such procedures performed annually in the United States has increased from 16,000 in the early 1990s to 103,000 in 2003, and this rise has continued. In Sweden, the prevalence of obesity has doubled over the last 20 years, and the number of obesity surgery procedures per year has increased from 1500 in 2006 to nearly 4000 in 2009.

It is well established that obesity surgery provides short- to medium-term benefits regarding diabetes and cardiovascular outcomes in obese individuals, but it is less clear how future cancer risk is affected. Previous studies addressing cancer risk have been relatively small or have described only a limited follow-up period after surgery. In our recent cohort study, an unexpected finding was that the risk of colorectal cancer seemed to increase with time after obesity surgery, whereas no such increase was found for the other main obesity-related cancers, including cancer of the breast, prostate, endometrium, and kidney. However, obesity is a recognized risk factor for colorectal cancer, and it was not possible to distinguish between colorectal cancer risk associated with excess body weight and that associated with previous obesity surgery.

In parallel, we have observed that putative mucosal biomarkers of colorectal cancer risk and mucosal proinflammatory gene expression were increased at least 3 years after Roux-en-Y gastric bypass obesity surgery compared with preoperative values.

The standardized incidence ratio (SIR) is the observed number of cases in a cohort divided by the expected number of cases for that group. The expected number is calculated by multiplying person's exposure time by the age-, sex- and calendar-year-specific incidence of a specific condition for the general “normal-risk” population. It is only possible to calculate an SIR accurately in countries such as Sweden that have detailed, complete population-level data. The use of the SIR gives a robust measure of relative risk for comparison of cohorts when the cohorts are not sufficiently well matched to allow direct case–control comparison.

We tested the hypothesis that obesity surgery is associated with increased colorectal cancer risk over extended (>10 years) periods of time, consistent with the long natural history of colorectal carcinogenesis. We achieved this by determining the SIR for colorectal cancer during follow-up after obesity surgery in a large number of obesity surgery patients with extended duration of follow-up after obesity surgery.

METHODS

Design

This was a Swedish nationwide retrospective cohort study of patients of at least 18 years of age, with a recorded diagnosis of obesity linked to a hospital admission, according to the Swedish Patient Register, during the period from January 1, 1980 to December 31, 2009. The start of the study period was selected on the basis that obesity surgery was not routinely conducted in Sweden before 1980. The end date was determined by the fact that the Swedish Patient and Swedish Cancer Registries were complete up to the end of 2009. Two cohorts were identified. The first cohort included all obese patients who had undergone obesity surgery as documented in the Swedish Patient Register. Obesity surgeries included vertical banded gastroplasty, adjustable gastric banding, and Roux-en-Y gastric bypass. In Sweden, obesity surgery has been offered only to patients with BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² with obesity-associated morbidity. The second cohort included all patients with a diagnosis of obesity who did not undergo obesity surgery according to the Swedish Patient Register. The study outcome was the time trends at the first occurrence of colorectal cancer (adenocarcinoma) as documented in the

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Swedish Cancer Register. The study was approved by the Regional Ethical Review Board in Stockholm.

**Data Collection**

The Swedish Patient Register was used to collect data on age, sex, Personal Identity Number (a unique 10-digit code assigned to each Swedish resident, allowing individual accurate linkage between registers), discharge diagnoses, surgical procedures, and hospitalization dates. The percentage of the Swedish population covered by this register was 85% in 1983, and 100% in 1987 and onward. The Swedish Patient Register has achieved 95% accuracy and 98% completeness regarding surgical procedures. The International Classification of Diseases (ICD) versions 8, 9, and 10 were used to identify patients with a diagnosis of obesity (277.99 in ICD-8, 278A in ICD-9, or E66 in ICD-10). The Swedish Classification of Operations and Major Procedures was used to identify patients undergoing obesity surgery (operation codes 4751–4753 before 1997, or codes JDF00-JDF01, JDF10-JDF11, and JDF20-JDF21 from 1997).

The Swedish Cancer Register was used to identify cases of colorectal adenocarcinoma (ICD-7 codes 153 and 154, and WHO/HS/CANC/24.1 histology code 096). The register includes the date of diagnosis, site of the tumor (all translated into ICD-7 codes), and histological type of malignant tumors diagnosed in Sweden since 1958. All physicians and pathologists are obliged to report all cancer cases, and the register has a minimum 96% nationwide completeness rate.

The Register of the Total Population was used to censor cohort members who died or emigrated during follow-up. These patients were censored from the date of first emigration or the exact date of death. This register has a 100% nationwide completeness and is constantly updated.

The Swedish Educational Register was used to collect data on the highest achieved educational level. This register is updated yearly by Statistics Sweden.

**Statistical Analysis**

The Swedish Personal Identity Number system and nationwide complete registers for cancer, mortality, and emigration in Sweden make it possible to calculate the SIR as a robust estimate of relative risk for both obesity surgery and obese no surgery cohorts, rather than perform a direct comparison between 2 very different cohorts, which would be confounded by significant differences in age and comorbidity. The risk of developing colorectal cancer with increasing follow-up time in the 2 study cohorts was compared with the expected risk as determined from the Swedish Cancer Register. The expected number of cases of colorectal cancer was calculated separately for the 2 study cohorts by multiplying the observed person-time by age- (3-year groups), sex-, and calendar-year-specific cancer incidence rates in the corresponding background population in Sweden. The SIR and 95% confidence interval (CI) were calculated as the ratio of the observed number of cases of colorectal cancer to the expected number. Person-years at risk in each cohort were accumulated until the occurrence of any of the following events: any cancer, death, emigration, or the end of the study period (December 31, 2009), whichever occurred first. All person-time during the first year after surgery was excluded to avoid detection bias, i.e., earlier detection of colorectal cancer because of obesity surgery or hospitalization.

Potential confounding by age, sex, and calendar year was minimized by the design, using a background comparator population matched for these variables. To evaluate confounding by excess alcohol use and by tobacco smoking, sensitivity analyses were conducted excluding all patients in the 2 study cohorts with a recorded diagnosis representing alcohol abuse or tobacco smoking in the Patient Register. Alcohol-related diagnoses included a history of excessive alcohol consumption (diagnosis code F10 in ICD-10, 291 or 303 in ICD-9 and ICD-8, or 307 or 322 in ICD-7) or vitamin B deficiency associated with alcohol (E51–52 or G62.1 in ICD-10, 265 in ICD-9, 261.00–262.00 in ICD-8, or 280–281 in ICD-7) or alcohol-related liver disease (K70 in ICD-10, 571.8 or 571.C in ICD-9, 571.00 or 571.01 in ICD-8, or 581.10 or 583.10 in ICD-7). Tobacco smoking-related diseases included chronic obstructive pulmonary disease or bronchitis (J41–J44 in ICD-10, 490–492 in ICD-9 and ICD-8, 501.99, 502, 527.10, or 527.11 in ICD-7) or atherosclerosis or peripheral vascular disease (170 or 173.9 in ICD-10, 440 or 443X in ICD-9, 440, 443.90 or 445 in ICD-8, or 450.00, 450.10, 453.33 in ICD-7).

**RESULTS**

**Patients**

A total of 15,095 patients were included in the obesity surgery cohort, and 62,016 patients were included in the obese no surgery cohort. During a median of 10 years (range 1–30 years) and 146,810 person-years of follow-up of the obesity surgery cohort, 70 new cases of colorectal cancer were identified. In the no surgery cohort, 373 such cases were observed during a median follow-up of 7 years (range 1–30 years) and 411,041 person-years at risk. Characteristics of the patients in the 2 cohorts are presented in Table 1. The majority of patients in both cohorts were female. Patients in the obesity surgery cohort had a lower mean age (39 years) than those in the obese no surgery cohort (49 years). The 2 cohorts were similar regarding the highest education level attained. Half of the obesity surgical procedures were restrictive, i.e., vertical banded gastroplasty or adjustable gastric banding, whereas the other half were malabsorptive, i.e., gastric bypass (Table 1). Diabetes, hypertension, and cardiovascular disorders were overrepresented in the obese no surgery cohort compared with the obesity surgery cohort, whereas the frequencies of respiratory, gastrointestinal, and psychiatric disorders were similar (Table 1).

**Risk of Colorectal Cancer**

The absolute cumulative incidence of colorectal cancer in the obesity surgery cohort was lower (48 per 100,000 person-years) than that of the obese no surgery cohort (91 per 100,000 person-years), which is likely due to a younger mean age in the surgery group. The overall SIR for colorectal cancer was 1.60 (95% CI: 1.25–2.02) in the obesity surgery cohort (Table 2). The corresponding SIR in the obese no surgery cohort was only slightly increased (SIR 1.26, 95% CI: 1.14–1.40). In the obesity surgery cohort, the risk of colorectal cancer increased with longer follow-up time after surgery (P for trend 0.05). For patients followed up for at least 10 years, the SIR was 2.00 (95% CI: 1.48–2.64). Unlike the obesity surgery cohort, the length of follow-up did not influence the SIR for colorectal cancer in the obese no surgery cohort (Table 2).

The SIR was higher in men than in women in both cohorts (Table 2). A longer follow-up after obesity surgery was associated with a gradually increased SIR in both men and women, whereas no such pattern was revealed for either men or women in the obese no surgery cohort. In men followed up for at least 10 years, the SIR after obesity surgery was 3.11 (95% CI: 1.88–4.86), whereas the SIR was 1.48 (95% CI: 1.06–2.02) in the obese no surgery cohort. The corresponding SIRs in women was 1.63 (95% CI: 1.10–2.32) in the obesity surgery cohort and 1.16 (95% CI: 0.90–1.48) in the obese no surgery cohort. Patients undergoing obesity surgery at a younger age had higher SIR point estimates of colorectal cancer compared with those operated on later in life, and among those operated on between the ages of 18 and 39 years, the SIR was 1.94 (95% CI: 1.09–3.20). There were no such age differences in the obese no surgery cohort (Table 2). The SIR in the obesity surgery cohort was not influenced by...
the type of surgical procedure or the need for more than one obesity surgical procedure (Table 2).

The sensitivity analysis excluding 1463 (9.7%) individuals with diseases related to alcohol abuse or tobacco smoking in the obesity surgery cohort did not change the results substantially; the trend of increased SIR with increased time after obesity surgery remained ($P$ for trend 0.01), and patients followed up for more than 10 years after surgery had an SIR of 1.63 (95% CI: 1.13–2.28) for developing colorectal cancer. In the obese no surgery cohort, the SIR remained virtually unchanged after exclusion of 9287 (15.0%) individuals with diseases related to alcohol abuse or tobacco smoking (data not shown).

Although based on limited sample sizes, the pattern of increased SIR with longer follow-up in the obesity surgery cohort, but not in the obese no surgery cohort, was also seen when analyzing the risk of colonic and rectal cancer separately (data not shown). Finally, because we used a part of the obesity surgery cohort for a previous analysis, we conducted a separate analysis of the data not available for that study and found similar point estimates for the SIR in the obesity surgery group, but the power was limited (data not shown).

**DISCUSSION**

This study indicates that obesity surgery is associated with an increased risk of colorectal cancer with increasing time after obesity surgery, whereas no such pattern was found in the obese patients who did not undergo obesity surgery. Methodological strengths of the current study include the cohort design, which counteracts selection bias, the large sample size, the length of follow-up (up to 30 years), and the high completeness and validity of the data afforded by the Swedish National Registers. By virtue of the Personal Identity Number system and the national, complete population Registries available in Sweden, we were able to calculate SIRs as valid estimates of relative risk of colorectal cancer in separate cohorts compared with the general population.

Retrospective Registry-based design also entails limitations, including the lack of data on individual BMI and changes in excess body weight over time in the 2 obese cohorts. BMI is, however, likely to be stable with time in the vast majority of nonoperated obese patients, as no other treatment than obesity surgery seems to offer a long-lasting weight reduction. A proportion of the patients in the obesity surgery cohort might not have lost any weight, but this frequency should be limited and would tend to dilute the risk estimates if weight loss is the reason for the increased risk of colorectal cancer. However, there are previously published BMI data on large subgroups of the individuals in the present study. The mean baseline BMI of 2010 patients in the surgery cohort was 42.4 kg/m$^2$ compared with a mean BMI of 40.1 kg/m$^2$ in 2037 patients in the obese no surgery cohort. Ten years after obesity surgery, the mean weight loss after vertical banded gastroplasty, adjustable gastric banding, and gastric bypass was 16 kg, 14 kg, and 25 kg, respectively. In obese individuals who did not undergo obesity surgery, body weight remained stable ($\pm 2\%$) during a 13-year observation period. The observation that the obese no surgery cohort had a stable, elevated SIR is consistent with the type of surgical procedure or the need for more than one obesity surgical procedure (Table 2).

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The increased risk of colorectal cancer found in this study is not in agreement with the potentially protective effects of bariatric surgery on overall cancer incidence found in other studies.9–11 The few studies that have previously assessed the overall risk of cancer after obesity surgery have not had sufficient statistical power or length of follow-up to reliably evaluate any specific changes in the risk of colorectal cancer.8–11 The studies that reported the number of colorectal cancer cases after obesity surgery found only 35, 25, and 2 cases.8,10,11 In a cohort study from the United States, a 30% statistically nonsignificant decreased risk of colorectal cancer was reported in patients after gastric bypass surgery compared with morbidly obese controls.10 However, the obese no surgery cohort members were selected and were not entirely comparable to patients in the obese surgery cohort, so that the obese no surgery group was likely to have more comorbidities and therefore at a higher baseline risk of cancer development. In the present study, the emergence of a substantial increase in colorectal cancer risk, above that associated with the known link between obesity and increased colorectal cancer risk,13,20,21 and indicates validity.

The obese no surgery cohort only represents a small part of the total number of obese people in Sweden because most of the cohort members received this diagnosis because of hospitalization for another disease. This cohort merely represents those who sought hospital care and incidentally had obesity, which is the likely explanation for the increased vascular and diabetes comorbidity compared with the obesity surgery cohort. Moreover, the age distribution of the obesity surgery cohort and of the obese no surgery cohort were very different. This makes direct comparison of the obese no surgery group with the obesity surgery cohort hazardous, and we never intended to formally compare these cohorts directly. However, the SIR trends with follow-up time in the 2 cohorts should not be influenced by such potential bias. Therefore, the main aim of the study was to assess the time trends regarding SIRs in the 2 cohorts. The excess colorectal cancer risk in the obesity surgery cohort is unlikely to be solely due to residual excess body weight after obesity surgery, given the increase in risk with time, and the absence of significant re-gain of body weight after surgery to values similar to obese individuals who did not undergo obesity surgery.3 Detection bias is another methodological issue that would occur if patients who had obesity surgery, or were hospitalized, underwent more gastrointestinal investigations than individuals in the general population. To reduce this concern, we excluded colorectal cancer outcomes in the first year after surgery, a standard practice in cohort studies of the present design, and the main study outcome addressed long-term effects after surgery rather than short-term outcomes. Moreover, the increased colorectal cancer risk apparent with longer follow-up in those who underwent obesity surgery would not be explained by such bias. Confounding is a threat to all observational research. Inherent adjustments for potential confounding by age, sex, and calendar year were, however, made in the analyses. Direct information on other risk factors, ie, alcohol overconsumption,22 tobacco smoking,23 physical inactivity,24 diabetes,25 and family history, or protective factors such as nonsteroidal anti-inflammatory drug use,26 were not available. Potential confounding by excess alcohol use and tobacco smoking was instead assessed indirectly through exclusion of persons hospitalized for diseases related to alcohol or tobacco. Such an assessment is not accurate and does not exclude residual confounding, but nevertheless, the results of the sensitivity analyses were similar to the unadjusted data, indicating no or limited confounding by these factors. Diabetes was not taken into account, but it is well established that the majority of patients undergoing obesity surgery achieve resolution of diabetes.6 Regarding confounding by heredity, there are no strong reasons to believe that patients undergoing obesity surgery would be more or less likely to have a family history of colorectal cancer than people in the general population of the corresponding age or other obese patients.

### TABLE 2. Risk of Colorectal Cancer, Expressed as the Standardized Incidence Ratio (SIR) With 95% Confidence Interval (CI), in the Obesity Surgery Cohort and the Obese No Surgery Cohort Identified in the Swedish Patient Register Between 1980 and 2009

<table>
<thead>
<tr>
<th>Colorectal Cancer</th>
<th>Obesity Surgery Cohort</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>SIR (95% CI)</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>1.60 (1.25–2.02)</td>
</tr>
<tr>
<td>Follow-up time, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>8</td>
<td>0.94 (0.41–1.86)</td>
</tr>
<tr>
<td>5–9</td>
<td>13</td>
<td>1.22 (0.65–2.09)</td>
</tr>
<tr>
<td>≥10</td>
<td>49</td>
<td>2.00 (1.48–2.64)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>2.17 (1.40–3.20)</td>
</tr>
<tr>
<td>Female</td>
<td>45</td>
<td>1.40 (1.02–1.87)</td>
</tr>
<tr>
<td>Age groups at entry into the cohorts, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–39</td>
<td>15</td>
<td>1.94 (1.09–3.20)</td>
</tr>
<tr>
<td>40–49</td>
<td>28</td>
<td>1.78 (1.18–2.57)</td>
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<tr>
<td>≥50</td>
<td>27</td>
<td>1.34 (0.88–1.94)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Obesity surgery procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertical banded gastroplasty</td>
<td>31</td>
<td>1.62 (1.10–2.30)</td>
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<tr>
<td>Adjustable gastric banding</td>
<td>27</td>
<td>1.63 (1.08–2.38)</td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>12</td>
<td>1.50 (0.78–2.62)</td>
</tr>
<tr>
<td>Number of obesity surgery procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>60</td>
<td>1.62 (1.24–2.09)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>10</td>
<td>1.50 (0.72–2.76)</td>
</tr>
</tbody>
</table>
with excess body weight alone, more than 10 years after surgery is compatible with the long natural history of colorectal carcinogenesis from normal mucosa to a malignant colorectal cancer. The higher risk of colorectal cancer in individuals after obesity surgery, who then have a lower BMI, than obese individuals who have not undergone obesity surgery further suggests that obesity surgery is the key risk exposure postoperatively rather than continuing excess body weight. It is not clear why previous obesity surgery would increase the risk of colorectal cancer, but we recently reported that patients who underwent gastric bypass exhibited rectal mucosal hyperproliferation that persisted at least 3 years after surgery. 13 This finding was associated with increased mucosal expression of the protumorigenic cytokine macrophage migration inhibitory factor. 13 Therefore, one hypothesis is that local mucosal changes secondary to the malabsorptive effects of the gastric bypass procedure explain the increased colorectal cancer risk. This could be due to increased mucosal bile salt exposure or changes in intestinal microbiota, which are both recognized after gastric bypass. 28, 29 Because there is no overall increased risk of obesity-related cancer after obesity surgery, 3–11 the rectal mucosal changes are compatible with the concept that increased cancer risk after obesity surgery may be restricted to the colorectum. Importantly, we found that the increased risk of colorectal cancer was similar for all 3 obesity surgery procedures, including vertical banded gastroplasty and adjustable gastric banding, which are both restrictive, rather than malabsorptive, surgical strategies. There are currently no studies that address changes in colorectal mucosal proliferation state or inflammation after gastroplasty or gastric banding, but a unifying hypothesis is that each of the obesity surgery procedures could lead to the promotion of colorectal carcinogenesis via altered colorectal metabolite profiles, secondary to changes to the gut microbiota, combined with modified dietary intake postoperatively. 28–30 For example, a diet high in protein is one of the cornerstone of postoperative nutritional care, 31, 32 but it has recently been shown that a high-protein, low-carbohydrate diet can promote detrimental metabolite profiles in the colorectum, including a decrease in short-chain fatty acid concentrations and increased exposure to N-nitroso compounds, both of which have been implicated in driving colorectal carcinogenesis. 33 Recently, it has been reported that alterations in the intestinal microbiota and fecal metabolite profile after Roux-en-Y gastric bypass in a rat model are associated with increased fecal cytotoxicity compatible with increased carcinogenicity. 34 This emphasizes that a complex interaction between the gut microflora and diet exists that could explain increased carcinogenic risk after obesity surgery. The effect of the different restrictive and malabsorptive obesity surgery procedures on the gut microbiota and colonic metabolite profiles deserves further investigation, particularly in view of recent observations that Bacteroides/Prevotella species are increased after gastric bypass 35 and Bacteroides/Prevotella species are higher in patients with colorectal cancer compared with body weight-matched controls. 36 Alternatively, the different obesity surgical procedures produce similar effects on gut hormone profiles, including increased peptide YY levels and reduced glucagon-like peptide-1 levels. 37, 38 Therefore, the effect of postsurgical neurohormonal modulation on long-term cancer risk also requires further investigation. 39 Whether weight gain often seen after obesity surgery influences the risk of colorectal cancer is unknown, but any effect of such weight gain on colorectal cancer risk and colorectal luminal changes needs to be evaluated in even larger studies with longer follow-up.

CONCLUSIONS

In conclusion, this large register-based cohort study, with long and complete follow-up, indicates that obesity surgery is associated with an increasing risk of colorectal cancer with time after surgery. It is established that obesity surgery provides several metabolic benefits in the short-to-medium term, 3, 4, 40 but our data suggest that increased colorectal cancer risk may be a long-term consequence of such surgery. If this association is confirmed, it should stimulate research addressing colonoscopic evaluation of the incidence of colorectal adenomatous polyps after obesity surgery with a view to defining an optimum colonoscopy surveillance strategy for the increasing number of patients who undergo obesity surgery.