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Obesity surgery and risk of colorectal and other obesity-related cancers: An English population-based cohort study

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ABSTRACT

Background: The association between obesity surgery (OS) and cancer risk remains unclear. We investigated this association across the English National Health Service. A population-based Swedish study has previously suggested that OS may increase the risk of developing colorectal cancer (CRC).

Methods: A retrospective observational study of individuals who underwent OS (surgery cohort) or diagnosed with obesity, but had no OS (no-surgery cohort) (1997–2013) were identified using Hospital Episode Statistics. Subsequent diagnosis of CRC, breast, endometrial, kidney and lung cancer, as well as time 'at risk', were determined by linkage to National Cancer Registration & Analysis Service and Office of National Statistics data, respectively. Standardised incidence ratios (SIR) in relation to OS were calculated.

Results: 1 002 607 obese patients were identified, of whom 3.9% (n = 39 747) underwent OS. In the no-surgery obese population, 3 237 developed CRC (SIR 1.12 [95% CI 1.08–1.16]). In those who underwent OS, 43 developed CRC (SIR 1.26 [95% CI 0.92–1.71]). The OS cohort demonstrated decreased breast cancer risk (SIR 0.76 [95% CI 0.62–0.92]), unlike the no surgery cohort (SIR 1.08 [95% CI 1.04–1.11]). Increased risk of endometrial and kidney cancer was observed in surgery and no-surgery cohorts.

Conclusions: CRC risk is increased in individuals diagnosed as obese. Prior obesity surgery was not associated with an increased CRC risk. However, the OS population was small, with limited follow-up. Risk of breast cancer after OS is reduced compared with the obese no-surgery population, while the risk of endometrial and kidney cancers remained elevated after OS.

1. Introduction

Obesity is linked to an increased risk of several malignancies, including colorectal (CRC) [1–3] post-menopausal breast [4–6], endometrial [7,8] and kidney cancers [9,10]. Obesity (also known as bariatric) surgery (OS) is an effective treatment for weight reduction providing metabolic and cardiovascular benefits[11]. In parallel with the increased prevalence of obesity, there has been a significant increase in the frequency of OS [12]. Traditional OS procedures such as gastric banding and Roux-en-Y gastric bypass (RYGB), which induce weight loss via restrictive and combined restrictive/malabsorbtive mechanisms respectively, are the most commonly performed worldwide [11]. Over the last decade, sleeve gastrectomy has emerged as an alternative procedure [11,13].

The effect of OS on future risk of CRC is not clear. Counterintuitively, there is evidence that OS may increase the long-term risk of developing CRC despite post-operative weight loss [14–17]. The effect appears to be time-dependent, with the risk of CRC increasing with time from surgery, which would be consistent with the long natural history of colorectal carcinogenesis. It is plausible that colorectal carcinogenesis may be driven by changes in diet and the gut microbiota post-bariatric surgery [18,19]. By contrast, a meta-analysis

Abbreviations: CRC, colorectal cancer; OS, obesity surgery; RYGB, Roux-en-Y gastric bypass; HES, Hospital Episode Statistics; ONS, Office of National Statistics; SIR, standardised incidence ratio; NCRAS, National Cancer Registration & Analysis Service

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of four observational studies, which have reported CRC incidence after OS, concluded that overall OS is associated with a 27% lower risk of subsequent CRC [20].

However, all studies to date, except one population-based Swedish study [14] have been limited in their follow-up time after OS (less than ten years) and sample size (so statistical power) to fully explore the association with incident CRC [21–23]. We aimed therefore, to confirm or refute the findings of the Swedish study in a separate independent population. We tested the hypothesis that there is an increase in CRC incidence following OS in a large population-based cohort of individuals who had undergone OS in England, also determining the risk of other obesity-related cancers for comparison.

2. Methods

2.1. Design

This was a national population-based retrospective observational data-linkage study of individuals over the age of 18 and below 95 years, who had an episode of in-patient or day-case care in an English NHS hospital involving a primary diagnosis of obesity or OS. Study approval was obtained from the Health Research Authority Confidentiality Advisory Group (CAG) (CAG reference: CAG 4-09(b)/2013) and Research Ethics Committee (REC reference: 13/YH/0204). This research was funded by World Cancer Research Fund International (WCRF) and Cancer Research UK (CRUK).

Patients diagnosed with obesity were identified using the International Classification of Diseases Version 10 (ICD10): E66 code. OS was defined as an episode of care with a primary diagnosis of obesity with an Office of Population Censuses and Surveys (OPCS) Classification of Interventions and procedures (4th revision) procedure code for a surgical procedure listed in Table 1. These individuals were identified using a Hospital Episode Statistics (HES) dataset containing hospital admissions between April 1997 and September 2013. We reviewed OPCS4 codes used by NHS Digital (previously the Health and Social Care Information Centre) in previous analyses and excluded several procedures that were either; 1) very unlikely to be performed as OS, or 2) were a revision, reversal or maintenance procedure [24,25]. Table 1 details the codes used by NHS Digital and the codes used in this study. If individuals within this cohort had multiple episodes of care of the same type recorded (OS or obesity without surgery), then the first episode of care took precedence. If an individual had both OS and obesity no surgery episodes recorded then the surgery episode was used.

The cohort was linked to the National Cancer Registration & Analysis Service (NCRAS) dataset to determine if these individuals received, subsequent to the index episode (OS or obesity alone), a diagnosis of CRC (ICD10 C18-C20), breast (ICD10 C50), kidney (ICD10 C64) or endometrial (ICD10 C54) cancer, which are all cancers known to be linked to obesity [14,16,26]. In contrast, lung cancer (ICD10: C33-C34) is not obesity-related [26] but was included as a control as its incidence should be unaffected by OS. Lastly, upper gastrointestinal cancers (esophageal cancer (ICD-10: C15), stomach cancer (ICD-10: C16), small intestine cancer (ICD-10: C17), liver cancer (ICD-10: C22), gallbladder cancer (ICD-10: C23), extrahepatic bile duct cancer (ICD10: C24) and pancreatic cancer (ICD10: C25)) were included in the data as the codes used to identify OS are similar to those used for surgical procedures used to manage these cancers. Individuals with upper gastrointestinal cancers were subsequently excluded from the analyses.

The cohort was linked to the Office for National Statistics (ONS) mortality dataset to determine individual time at risk of cancer diagnosis. This was defined as the time from the index episode to cancer diagnosis, death or the censor date (30th September 2013).

The characteristics of the groups who did and did not undergo OS, subsequently referred to as surgery and no-surgery cohorts, were compared. This revealed a relatively high proportion of individuals that apparently underwent OS a short period after a diagnosis of cancer. These operations were likely to be associated with cancer management rather than to treat obesity. Thus, all individuals who developed a cancer within one year of the index episode were excluded.

2.2. Statistical analysis

The standardized incidence ratio (SIR) with 95% confidence interval (CI) was calculated as an estimate of relative risk of both surgery and no-surgery obese participants diagnosed with a cancer instead of making a direct comparison between the two cohorts that could be confounded by differences in age, calendar year and other risk factors. The SIR was calculated as the ratio of the observed number of cancer cases in the study population to the number that would be expected if that population experienced the same cancer incidence rates as the background English population, dependent on age and calendar period. This was achieved by splitting follow-up time into one-year age categories and one-year calendar periods and each age-period-sex group was then linked with cancer incidence rates in England obtained from NCRAS. The expected number of cancer cases was calculated for both the surgery and no-surgery cohorts by multiplying the observed person time by age, sex and calendar year-specific cancer incidence rates for England. The follow-up time after OS was classified as: 1 to 2 or ≥ 2 years. All person-time during the first year after surgery or diagnosis of obesity was excluded because of the risk of erroneous identification of procedures associated with cancer resection or palliation, rather than OS, or earlier detection of CRC due to hospitalization or obesity surgery. This widened exclusion by reducing all individuals' risk time by one year, and not only those who were diagnosed with cancer within one year from the index event. Finally, the observed and expected numbers of deaths were summed and divided. The SIR with 95% CI was estimated under the assumption that the observed number of events followed a Poisson distribution.

3. Results

3.1. Patients

A total of 1 056 392 patients were initially identified. After exclusions, the final dataset consisted of 1 002 607 individuals, including; 39 747 (3.9%) recorded as having OS and the remainder (962 860; 96.0%) as having an episode of hospital care due to obesity without OS (Fig. 1). Table 2 details the characteristics of the two groups. The majority of patients in both groups were female; 76.6% in the OS group and 62.9% in the obese no OS group. The OS group was younger than the no surgery group, with a mean age of 44.8 and 53.1 years, respectively. The majority of OS (91.7%) took place after 2006 and this restricted the potential follow-up time after surgery to six years for the majority of this population. The OS group had a median follow-up period of 3.0 years (range 1–16 years) and 144 677 person-years of follow-up. The equivalent figures for the obese no OS group were a median follow-up time of 2.5 years (range 1–16 years) and 3 608 882 person-years at risk.

3.2. Risk of colorectal cancer

There were 43 new diagnoses of CRC in the OS group and 3 237 new diagnoses in the obese no OS group. Table 3 shows the SIR for CRC diagnosis in the two groups, after exclusion of all person-time within one year from the OS surgery or hospital attendance associated with obesity. Comparisons were not made directly between the two groups, but between each group and the English background population. The absolute cumulative incidence of CRC in the surgery group was lower (30 per 100 000 person-years) than that in the no surgery group (91 per 100 000 person-years), which is likely explained by the younger age of the surgery cohort. The overall SIR for CRC in the surgery cohort was not significantly increased compared to the background English