Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Long-term incidence of female-specific cancer after bariatric surgery or usual care in the Swedish Obese Subjects Study

Åsa Anveden [a,b,1], Magdalena Taube [a,1], Markku Peltonen [c], Peter Jacobson [a], Johanna C. Andersson-Assarsson [a], Kajsa Sjöholm [a], Per-Arne Svensson [a,d,*], Lena M.S. Carlsson [a]

[a] Department of Molecular and Clinical medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[b] Department of Surgery, Hallands Hospital, Halmstad, Sweden
[c] Department of Chronic Disease Prevention, National Institute of Health and Welfare, Helsinki, Finland
[d] Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

HIGHLIGHTS

- Bariatric surgery is associated with reduced risk of overall female-specific cancer.
- Treatment benefit of bariatric surgery is greatest in women with hyperinsulinemia.
- Bariatric surgery is associated with reduced risk of endometrial cancer.

ARTICLE INFO

Article history:
Received 29 December 2016
Received in revised form 14 February 2017
Accepted 22 February 2017
Available online xxxx

Keywords:
Female-specific cancer
Gynecological cancer
Endometrial cancer
Obesity
Bariatric surgery

ABSTRACT

Objective. To examine the long-term effects of bariatric surgery on female-specific cancer in women with obesity.

Methods. The prospective, matched Swedish Obese Subjects (SOS) study was designed to examine outcomes after bariatric surgery. This study includes 1420 women from the SOS cohort that underwent bariatric surgery and 1447 contemporaneously matched controls who received conventional obesity treatment. Age was 37–60 years and BMI was ≥38 kg/m^2. Information on cancer events was obtained from the Swedish National Cancer Registry. Median follow-up time was 18.1 years (interquartile range 14.8–20.9 years, maximum 26 years). This study is registered with ClinicalTrials.gov, NCT01479452.

Results. Bariatric surgery was associated with reduced risk of overall cancer (hazard ratio = 0.71; 95% CI 0.59–0.85; $p < 0.001$). About half of the observed cancers were female-specific, and the incidence of these were lower in the surgery group compared with the control group (hazard ratio = 0.68; 95% CI 0.52–0·88; $p = 0.004$). The surgical treatment benefit with respect to female-specific cancer was significantly associated with baseline serum insulin (interaction p value = 0.022), with greater relative treatment benefit in patients with medium or high insulin levels. Separate analyses of different types of female-specific cancers showed that bariatric surgery was associated with reduced risk of endometrial cancer (hazard ratio = 0.56: 95% CI 0.35–0.89; $p = 0.014$).

Conclusions. In this long-term study, bariatric surgery was associated with reduced risk of female-specific cancer, especially in women with hyperinsulinemia at baseline.

Funding. This project was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number R01DK105948 (the content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health), the Swedish Research Council K2013-99X-22279-01, K2013-54X-11285-19, Sahlgrenska University Hospital ALF research grant and Swedish Diabetes Foundation.

* Corresponding author at: Sahlgrenska University Hospital, Vita Stråket 15, S-413 45 Gothenburg, Sweden.
E-mail address: Per-Arne.Svensson@medic.gu.se (P.-A. Svensson).
[1] Å.A. and M.T. contributed equally to this work.

http://dx.doi.org/10.1016/j.ygyno.2017.02.036
0090-8258/

1. Introduction

It is well known that obesity is associated with an increased risk of cancer [1–4]. Considering the high obesity prevalence, with >600 million people affected globally in 2014 [5], obesity is an important risk factor for cancer. In a recent study, 3.6% of all new cancer cases in adults were attributable to excess body weight, with a greater fraction in women (5.4%) than in men (1.9%) [6]. Obesity is also associated with more advanced cancer disease and increased cancer mortality [7]. In addition, various cancers, including endometrial and pancreatic cancer, are associated with type 2 diabetes, a common co-morbidity related to obesity [8].

Bariatric surgery is the most effective treatment for achieving sustainable weight loss in patients with obesity and it reduces the risk for morbidity and mortality [9–12]. Specifically, bariatric surgery has been shown to reduce the overall cancer risk in patients with obesity [13, 14]. In 2009 we reported that bariatric surgery was associated with reduced incidence of cancer in the Swedish Obese Subjects (SOS) study, an ongoing, non-randomized, prospective, controlled intervention trial investigating long-term effects of bariatric surgery [15]. We found that the cancer-preventive effect of bariatric surgery was seen in women, whereas there was no effect in men; an observation that has also been reported by Adams et al. [13]. In our previous report, the low incidence rate of specific cancers prevented a more detailed analysis. However, in the current study, with a median follow-up time of 18.1 years, we have a larger number of cancer events. The aim of this study was to further investigate the association between bariatric surgery and cancer in women, with focus on female-specific cancer, i.e. breast cancer and gynaecological cancers.

2. Methods

2.1. The SOS study

The SOS study is an ongoing, prospective matched intervention trial comparing bariatric surgery with conventional obesity treatment [9]. The study has been registered at ClinicalTrials.gov, identifier: NCT01479452. In brief, the study enrolled 4047 patients with obesity recruited through campaigns in mass media and at surgical departments and primary health care centres in Sweden between September 1, 1987 and January 31, 2001. The current analyses include women only. Inclusion criteria were: aged 37–60 years and a BMI >38 kg/m^2. Exclusion criteria, identical in surgery and control groups, were minimal and aimed at obtaining an operable surgical group. Matching of the control group and surgery group was performed on group level using 18 matching variables [16]. The intervention study began on the day of surgery for both the surgically treated individual and the matched control.

Seven regional ethics review boards approved the SOS study protocol, and informed consent was obtained from all participants. The primary endpoint of the study was overall mortality, which was reported in 2007 [9]. The secondary endpoints were diabetes [17], gallbladder disease [18], and cardiovascular disease [12]. The outcome of the current study, cancer incidence, was not a predefined endpoint.

2.2. Intervention

Among the 1420 women in the SOS surgery group, 260 (18.3%) underwent non-adjustable or adjustable gastric banding, 970 (68.3%) underwent vertical banded gastroplasty, and 190 (13.4%) underwent gastric bypass. Women in the control group (n = 1447) received the conventional treatment for obesity at their primary health care centre, ranging from advanced life-style advice to basically no professional treatment at all.

2.3. Examinations

Surgery and control participants underwent a baseline examination approximately four weeks before the start of intervention. Thereafter clinical examinations were carried out after 0.5, 1, 2, 3, 4, 6, 8, 10, 15 and 20 years. Centralized biochemical examinations were carried out at matching and baseline examinations, and after 2, 10, 15 and 20 years. Questionnaires were filled out at every clinical examination.

2.4. Data collection

Baseline characteristics were obtained from the clinical examination, questionnaires and centralized blood chemistry. Baseline alcohol intake was calculated from dietary questionnaires, as previously described [19]. Postmenopausal state was defined as a negative answer to the question: “Do you still menstruate?”, or time for surgical menopause. Smoking was defined as a positive answer to the question: “Do you smoke daily?” Data on cancer incidence, death and emigration were obtained by cross-checking social security numbers from the SOS database with the Swedish National Cancer Registry, the Cause of Death Registry and the Registry of the Total Population. The Swedish National Cancer Registry has over 95% coverage for all malignant tumours of which 99% are morphologically verified [20]. All malignant tumour diagnoses in the Swedish Cancer Registry were included. Female-specific cancer includes breast, endometrial, ovarian, cervix and all other gynaecological cancers. The cut-off date for the current report was December 31, 2013.

2.5. Statistical analysis

To describe baseline characteristics, mean values and standard deviations were used. All *p*-values are two-sided and *p* values of <0.05 were considered to indicate statistical significance. Statistical analyses were carried out using Stata version 12·1.

Comparisons between the surgery and the control group were done with one-way ANOVA for continuous variables and Fisher's exact test for dichotomous or discrete variables. To analyse cancer incidence, Kaplan-Meier estimates of cumulative incidence rates were used to compare time to first cancer diagnosis between different treatment groups. Furthermore, Cox proportional hazards models were used to calculate hazard ratios for surgical treatment for overall cancers and female-specific cancer i.e. breast, ovary, endometrial, cervix and other gynaecological cancers. No adjustments were made for multiple comparisons. To assess the impact of baseline differences between the surgery and control group, analyses were adjusted for baseline confounders; age, BMI and smoking status. The number needed to treat (NNT) to prevent one cancer event during 10 years was estimated by calculating the reciprocal of the absolute risk reduction. A per protocol approach was used in all analyses; thus, all participants were included in their original study group until any bariatric surgery was performed in the control group or there was a change in, or removal of, the bariatric surgical procedure in the surgery group, after which they were censored from the analysis.

In the interaction analysis, the incidence rates were calculated in subgroups defined by risk factors at baseline. The subgroups were based on tertiles of insulin, BMI, blood glucose or glucose status at baseline (normoglycemia, impaired fasting glucose or type 2 diabetes). The influence of bariatric surgery on the incidence of cancer events was tested by including the corresponding interaction term [i.e. product of type of treatment (surgery or control), and the corresponding continuous variable] in the Cox proportional hazard model.

To account for undiagnosed cancer at baseline, separate analyses were performed excluding cancer events occurring during the first three years of the study. In an additional sensitivity analysis, women that had undergone hysterectomy and/or oophorectomy before study start were excluded.

Please cite this article as: Å. Anveden, et al., Long-term incidence of female-specific cancer after bariatric surgery or usual care in the Swedish Obese Subjects Study, Gynecol Oncol (2017), http://dx.doi.org/10.1016/j.ygyno.2017.02.036