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Intentional weight loss, weight cycling, and endometrial cancer risk: A systematic review and meta-analysis

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Abstract

Purpose: Weight cycling, defined as intentional weight loss followed by unintentional weight regain, may attenuate the benefit of intentional weight loss on endometrial cancer risk. We summarized the literature on intentional weight loss, weight cycling after intentional weight loss, bariatric surgery, and endometrial cancer risk.

Methods: A systematic search was conducted using MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases published between January 2000 and November 2018. We followed Preferred Reporting Items of Systematic Reviews and Meta-analysis guidelines. We qualitatively summarized studies related to intentional weight loss and weight cycling due to the inconsistent definition and quantitatively summarized studies when bariatric surgery was the mechanism of intentional weight loss.

Results: A total of 127 full-text articles were reviewed, and 13 were included (bariatric surgery n=7, self-reported intentional weight loss n=2, self-reported weight cycling n=4). Qualitative

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AUTHOR CONTRIBUTION
XZ, JR, and ASF conceived of the study design, XZ and JR conducted the literature search, screening, data extraction, XZ and ASF analyzed the data, XZ, BJC, EDP and ASF wrote the first draft of the study, DEC, RS, SN, and AAS helped interpret data and provided critical revisions of the manuscript. All authors reviewed and approved the manuscript.

CONFLICT OF INTEREST
All authors declare no conflicts of interest.

synthesis suggested that compared to stable weight, self-reported intentional weight loss was associated with lower endometrial cancer risk (RR range=0.61–0.96), whereas self-reported weight cycling was associated with higher endometrial cancer risk (OR range=1.07–2.33). The meta-analysis yielded a 59% lower risk of endometrial cancer following bariatric surgery (OR=0.41, 95% CI=0.22, 0.74).

Conclusions: Our findings support the notion that intentional weight loss and maintenance of a stable, healthy weight can lower endometrial cancer risk. Strategies to improve awareness and maintenance of weight loss among women with obesity are needed to reduce endometrial cancer risk.

Keywords

intentional weight loss; weight cycling; endometrial cancer risk; systematic review and meta-analysis

INTRODUCTION

Obesity is an established risk factor for endometrial cancer, conferring a two to five times higher risk compared to healthy weight women[1,2]. As the prevalence of obesity has risen over the past four decades, parallel increases in endometrial cancer incidence have occurred[3]. Empirical data suggest an inverse association between weight loss and endometrial cancer risk[4]. However, prior studies have typically not distinguished between intentional vs. unintentional weight loss. Unintentional weight loss is associated with increased morbidity and could be a consequence of malignancy[5,6], while intentional weight loss, as a result of behavioral changes (e.g., a calorie-restricted diet with physical activity) or bariatric surgery, could improve body composition, improve metabolic and hormonal regulations, and favorably affect biological pathways, resulting in lower risk of endometrial cancer development[7–10].

The usual trajectory of intentional weight loss is followed by unintentional weight re-gain[11,12]. Weight cycling occurs when weight re-gain follows intentional weight loss in repeated cycles. In addition, weight cycling is more likely to result in redistribution of body fat to upper body subcutaneous adipose tissue and visceral fat[13], which may attenuate the benefit of intentional weight loss and increase endometrial cancer risk. Bariatric surgery, an effective weight loss treatment, results in substantial weight loss that is sustainable for 10–15 years[14,15]. Moreover, bariatric surgery is associated with a 46–60% lower endometrial cancer risk[16–18]. The rapid changes in body composition and extensive weight loss from bariatric surgery differ from the gradual changes induced by behavioral approaches for weight loss. On average, behavioral weight loss interventions result in 7–15% of body weight loss within 1–2 years, while bariatric surgery results in 15–35% of weight loss within 12 months[15,19]. The substantial weight loss within a short period can provide health benefits to individuals with obesity, especially patients with morbid obesity who experience difficulties in losing weight through behavioral interventions.

Previous reviews reported the association of bariatric surgery and lower risk of endometrial cancer[18,20]. However, no systematic review or meta-analysis has summarized data on self-reported intentional weight loss and self-reported weight cycling after intentional weight loss in relation to endometrial cancer risk. We summarized this literature to assess the hypotheses that intentional weight loss is associated with lower endometrial cancer risk while weight cycling after intentional weight loss is associated with increased endometrial cancer risk. We also provide an updated synthesis of the literature on bariatric surgery and endometrial cancer risk.

MATERIALS AND METHODS

Search strategy

This study was conducted following the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) guidelines[21]. Literature searches were conducted to evaluate the impact of 1) self-reported intentional weight loss, 2) self-reported weight cycling followed by intentional weight loss, and 3) bariatric surgery on endometrial cancer risk. Searches were carried out from January 2000 to November 2018 using MEDLINE via Ovid, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) databases. We performed a topic-specific search by combining Medical Subject Headings (MeSH) and non-MeSH keyword terms. Our search strategy captured a comprehensive set of key terms and Medical Subject Headings pertaining to the following subjects: endometrial cancer (including uterine, neoplasm, carcinoma, malignancy, adenocarcinoma etc.), intentional weight loss strategies (including various bariatric surgeries, behavioral strategies such as diet, caloric restriction, physical activity/exercise), and weight management/control. A list of search terms used for the three databases (MEDLINE, Embase, and CENTRAL) is included in the supplementary (S1 Figure a, b, c).

Criteria for selection of studies for this review

We included all published randomized clinical trials, non-randomized trials, and observational studies evaluating any intentional weight loss (bariatric surgery or self-reported intentional weight loss) and endometrial cancer risk. Reviews, case reports, letters, commentaries, editorials, unpublished studies, or any studies not published in English were not included.

Eligible studies were those that included female participants aged 18 years or older and those that excluded participants who had preexisting endometrial or uterine cancer before intentional weight loss. Our original plan was to classify intentional weight loss as a result of surgical procedures (bariatric surgery) or behavioral interventions (caloric restricted diet with or without increased physical activity). However, the lack of long-term follow-up after behavioral weight loss interventions hindered our ability to assess the risk of developing endometrial cancer. Therefore, this systematic review and meta-analysis evaluated the relationship between self-reported intentional weight loss, self-reported weight cycling after intentional weight loss, bariatric surgery, and endometrial cancer risk. Information on self-reported intentional weight loss and weight cycling were collected through self-reported questionnaire. Bariatric procedures included Roux-en-Y gastric bypass, gastric banding, vertical banded gastroplasty, vertical sleeve gastrectomy, jejunoileal bypass, and biliopancreatic diversion. We excluded studies if: 1)the weight loss was through pharmaceutical interventions; 2)the study endpoint was not a diagnosis of endometrial cancer (e.g. endometrial cancer-related biomarkers); 3) the diagnosis of endometrial cancer was prior to or during bariatric surgery or weight loss; and 4) did not include a control group. The primary outcomes of incidence, risk ratio, odds ratio, hazard ratio, or risk difference for endometrial cancer were assessed for each study.

Data extraction

Titles and abstracts of the initial search were assessed for eligibility by two independent investigators (XZ and JR). Duplicates were removed, and articles that did not meet the inclusion criteria were excluded. Full-text articles were assessed for eligibility by XZ and JR. For studies examining the association between self-reported weight cycling, self-reported intentional weight loss and endometrial cancer risk, we extracted author's last name, year of study, study type, population, study design, recruitment year, endometrial cancer diagnosis year, weight status measurement, weight cycling/weight loss definition, number of endometrial cancer cases, total sample size, comparison group and related effect estimate (e.g. odds ratio, relative risk, hazard ratio) with confidence intervals, and adjusted covariates (if any). For studies examining the association between bariatric surgery and endometrial cancer risk, we extracted author's last name, year of study, study type (e.g., case-control, cohort), population, study period, comparison groups, number of cases and controls for each group, total sample size, average age of participants, and included surgical procedures.

The quality and risk of bias of each study were assessed using the Newcastle-Ottawa quality assessment scale for cohort or case-control studies[22]. Study quality assessments were conducted independently by XZ and JR. Any discrepancies regarding inclusion, exclusion and risk assessment were resolved by consensus (XZ, JR, and ASF).

Data analysis

Eligible studies were classified into two groups: self-reported intentional weight loss/weight cycling or bariatric surgery. Descriptive characteristics were reported for all studies. A qualitative synthesis was conducted for studies examining self-reported intentional weight loss, weight cycling, and endometrial cancer risk. In the meta-analysis of bariatric surgery studies, we calculated the pooled effect estimate using a random effect model due to the high likelihood of between-group heterogeneity. The heterogeneity of effect size estimates across studies was quantified using the I^2 statistic, and the publication bias was assessed using the Egger's and Begg's tests[23]. All statistical analyses were completed using Stata MP Version 14.2 (StataCorp, College Station, TX).

RESULTS

Study selection

A total of 2,129 articles were identified through MEDLINE, Embase and Cochrane trial databases after duplicates were removed. After reviewing titles and abstracts, 127 full-text articles were assessed for eligibility, of which 114 were excluded for not meeting the eligibility criteria, leaving 13 eligible studies for review. Four articles examined self-reported weight cycling and endometrial cancer risk[24–27], two articles examined self-reported intentional weight loss and endometrial cancer risk[28,29], and seven articles examined bariatric surgery and endometrial cancer risk[14,17,30–34] (Figure 1). Among the 13 included articles, endometrial cancer cases were identified through state or national cancer registries, or the combination of self-report with linkage to medical records or cancer registries.

Study characteristics

Self-reported intentional weight loss and endometrial cancer risk were examined in two prospective cohort studies with follow-up time ranging between 14 and 22 years[28,29]. A total of 58,500 participants were included in these studies, among whom 708 developed endometrial cancer. Prior weight loss was classified as intentional or unintentional weight loss and assessed by a follow-up questionnaire administered six years after baseline[28] or measured using a standardized approach at clinic visits at baseline and three years after enrollment[29]. The cut point denoting self-reported intentional weight loss differed between the two studies, with Luo et al. using 10 pounds and Parker et al. using 20 pounds (Table 1a)[28,29].

Of four studies on self-reported weight cycling and endometrial cancer risk, two were prospective cohort studies with follow-up ranging from 15 to 21 years[25,27] and two were population-based case-control studies[24,26]. Data regarding weight cycling were collected from telephone or self-administered questionnaire. The time interval for weight regain varied: two studies examined regain within 12 months[24,26], one study defined the regain occurring during adulthood[27], and one study did not specify the time interval of the regain[25] (Table 1a). Among 92,063 participants involved in these studies, 3,485 cases of endometrial cancer were identified. One study did not report the number of endometrial cancer cases by weight cycling status[27]. Among weight cyclers (n=21,868), 831 (3.8%) endometrial cancer cases were identified, compared to 1,698 (8%) endometrial cancer cases identified among non-weight cyclers (n=21,225).

Of seven studies that evaluated the association between bariatric surgery and endometrial cancer risk, six were retrospective cohort studies with the recruitment period ranging between 4 and 26 years[17,30–34] and one was a prospective cohort study with follow-up spanning 26 years[14]. Four studies used frequency or propensity score matching of bariatric surgery patients to obese patients without bariatric surgery on baseline body weight or body mass index (BMI) distribution[14,17,31,34], while three did not employ matching[30,32,33]. There were a total of 7,455,757 participants involved in these studies comprising mainly patients with morbid obesity, ranging in age from 39 to 52. In these studies, a total of 44,404 cases of endometrial cancer were identified. Among women who did not have bariatric surgery (n=7,348,127), 43,541 (0.6%) cancers were identified, compared to 487 (1.9%) cases among women who underwent bariatric surgery (n=25,619). The bariatric surgical procedures were collected from surgical registry, patient registry, medical records of inpatient admissions, and health insurance database (Table 1b).

Synthesis of results

We used a qualitative synthesis for the two studies on self-reported intentional weight loss and endometrial cancer risk, due to the inconsistent cut points of weight loss and stable weight. Compared to those with stable weight, women reporting intentional weight loss of ten or more pounds were less likely to have a diagnosis of endometrial cancer. One study showed a 39% reduced risk (HR=0.61, 95% CI=0.40–0.92) associated with weight loss of 10 or more pounds within the last two years[29] and one showed a non-significant 4% reduced risk (RR=0.96, 95% CI=0.61–1.52)[28] associated with self-reported weight loss of 20 pounds at any point during adulthood (Table 2).

Due to the inconsistent definition of the weight cycling cut point, a qualitative synthesis was used for the four studies on self-reported weight cycling and endometrial cancer risk. Overall, the findings suggest that women who reported any weight cycling were more likely to have a diagnosis of endometrial cancer. Three studies showed weight cycling was significantly associated with 1.23–2.33 times increased endometrial cancer risk[24,26,27]; while one study showed a similar magnitude of association without statistical significance[25] (Table 2).

Data from five of seven articles on bariatric surgery and endometrial cancer risk were included in the quantitative synthesis using meta-analysis[14,30,31,33,34]. One article was excluded due to the use of an external comparison group (e.g., national age-standardized rate of endometrial cancer)[32]. In this study, the standardized incidence rate of endometrial cancer comparing bariatric surgery study participants to the Swedish age-standardized rate was 2.15 (95% CI=1.62–2.81). Another article was excluded due to lack of information regarding numbers of endometrial cancers according to bariatric surgery status; bariatric surgery was associated with lower endometrial cancer risk in this study (HR=0.50, $P<0.05$) [17]. The quantitative synthesis of the five studies demonstrated a 59% lower odds of endometrial cancer among women who had bariatric surgery compared to women who did not (pooled OR=0.41, 95% CI: 0.22, 0.74). In addition, significantly lower endometrial cancer risk, ranging from 19–80% risk reduction, was observed in the individual studies (Figure 2).

Quality assessment across studies

Study quality was assessed separately for the case-control and cohort studies and summarized according to participant selection, comparability across studies, and aspects related to outcomes (Table 3). The Newcastle-Ottawa Quality Assessment Scale ranges from 0–9 with a higher score indicating higher quality. In this review, the total scores of the 13 studies ranged from 6–9. Overall, studies of bariatric surgery and endometrial cancer risk were generally of higher quality compared with studies of self-reported intentional weight loss or weight cycling.

Among the two studies on self-reported intentional weight loss and endometrial cancer risk, weight loss was measured through a self-reported questionnaire in one study[28] and in the other, objectively measured weight at two time points was used[29]. One study did not account for hysterectomy status during the study period, and loss to follow-up was more than 20%[28]. Among the four studies on self-reported weight cycling and endometrial cancer risk, quality assessments were similar across studies. One study used controls recruited from two sources, including an endometrial cancer study and an ovarian cancer study, which may introduce selection bias[26]. All studies measured weight cycling once, and none of the studies specified the lag between the time of weight cycling and the time of endometrial cancer diagnosis. Although analyses in self-reported weight cycling studies all adjusted for BMI, no study matched for weight or BMI distribution between weight cyclers and controls, potentially leading to residual confounding by weight/BMI.

Of the seven studies examining bariatric surgery and endometrial cancer risk, one study used age- and calendar year-standardized rates of endometrial cancer as the comparison group[32] potentially leading to selection bias for the controls. One study did not report endometrial cancer status at baseline[33], and one did not specify whether participants had a hysterectomy at baseline[17]. Four studies specified the time lag (6 months, 1 year, 3 years, and 5 years) between bariatric surgery and endometrial cancer diagnosis, which allowed enough follow-up time to ascertain the outcome and minimize the impact of pre-existing cancer[14,17,31,34]. In addition, studies matched for weight or BMI distribution between bariatric surgery and non-surgical control groups reduced unmeasured confounding due to weight/BMI[14,17,31,34].

DISCUSSION

Findings from this review of observational studies support the notion that intentional weight loss is associated with lower endometrial cancer risk. However, weight cycling after intentional weight loss was linked with higher endometrial cancer risk. Our findings of increased endometrial cancer risk among weight cyclers demonstrate an important public health implication: avoidance of weight gain and maintenance of previous weight loss is critical for endometrial cancer prevention. Thus, strategies to sustain weight loss are needed to overcome the common trend of weight regains following intentional weight loss.

Bariatric surgery has been linked with lower overall cancer incidence and reduced risks of colorectal and breast cancers [35–37]. Consistent with two published meta-analyses, our study showed intentional weight loss through bariatric surgery was associated with lower endometrial cancer risk[18,20]. We included three recent studies on bariatric surgery and endometrial cancer risk that were not included in the previous reviews[14,17,34]. However, we excluded two studies from the Winder et al. review[20]: one study included 8 of 9 endometrial cancers diagnosed during the bariatric surgery[38] and the other did not distinguish women with previous cancer diagnosis or hysterectomy[39]. In addition, we excluded a recent study that used standardized incidence ratios to evaluate endometrial cancer risk for surgery and non-surgery patients with obesity compared to an external population[40]. In this study, the surgery group had an unexpectedly higher increased risk of endometrial cancer compared to the risk in the non-surgery group.

A recent meta-analysis of randomized controlled trials demonstrated favorable effect of weight loss interventions on risk of cardiovascular disease and cancer, without reaching statistical significance [41]. Other review articles showed intentional weight loss was associated with lower breast cancer risk, improved cardiovascular health, reduced risk of cardiovascular diseases and lower risk of liver diseases [42–44]. However, the common trajectory of intentional weight loss is followed by weight re-gain. We are the first to synthesize the association between self-reported weight cycling after intentional weight loss and endometrial cancer risk. The findings from included studies consistently suggest that weight cycling is related to increased endometrial cancer risk; however, the definition of self-reported weight cycling varied across studies as did the comparison group used for analysis. The inconsistent definition of weight cycling was also found in studies of other disease sites and study endpoints, such as cardiometabolic diseases, overall cancer risk, and mortality, which limited the possibility to quantify the pooled risk-estimates across studies [45–48]. It is critical to define a clinically meaningful threshold for the amount and timing of weight cycling and self-reported intentional weight loss. Perhaps using 5% or 10% weight loss in addition to the absolute weight change should be examined to account for individual variations in body weight. Furthermore, use of a consistent reference group would allow for meaningful comparisons of studies. Weight cycling is associated with redistribution of body fat to visceral fat[13,49], which is associated with elevated risk of endometrial cancer[50]. Future studies should investigate whether the elevated endometrial cancer risk from weight cycling is due to increased visceral fat, which can help researchers better understand underlying biological mechanisms.

Biological mechanisms linking obesity and endometrial cancer are mainly attributed to hormonal imbalances[51]. About 80% of endometrial cancers are thought to arise because of estrogen excess or progesterone deficiency[51]. Obesity alters systemic levels of insulin-like growth factors (IGFs) and hyperinsulinemia, all of which play a role in the pathogenesis of endometrial cancer[52,53]. In addition, obesity is characterized by low-grade inflammation with elevations in circulating pro-inflammation cytokines and acute phase proteins, such as CRP, TNF-alpha, soluble TNF receptors 1 and 2, IL-6, and IL-1 RA[54,55]. These serum biomarkers are consistently associated with increased endometrial cancer risk[7,9,10].

Observational studies suggest that weight loss may reverse the hormonal and metabolic imbalances associated with obesity and insulin resistance by reducing CRP, TNF-alpha, and IL-6 in the general population[8]. Behavioral weight loss interventions could normalize endometrial cancer-associated biomarkers, such as growth hormone, adiponectin, IL-6, IL-7, CA-125, and IGFBP-1, among women with severe obesity[56]. Similar findings were observed among women undergoing bariatric surgery[57,58]. In addition, resolution of endometrial hyperplasia was observed in 10 of 14 women 12 months following the bariatric surgery[58–60]. Taken together, results from biological studies of weight loss and endometrial cancer-associated biomarkers and our review of weight loss and endometrial cancer risk, indicate that endometrial cancer risk can be reduced by behavioral and surgical weight loss intervention.

We originally proposed to compare the effect of behavioral weight loss interventions (*e.g.*, calorie restricted diet with or without physical activity prescription) to surgical weight loss intervention on endometrial cancer risk. We hypothesized that the mechanism of gradual weight loss through healthy eating and increased physical activity differs from the substantial and rapid weight loss through invasive surgical procedures. However, we only identified one article of a behavioral weight loss intervention, but this study used endometrial cancer-associated biomarkers as endpoints instead of cancer occurrence [56]. Results from the Look AHEAD study, which includes 5,145 participants with 12 years of follow-up after a behavioral intervention, are forthcoming[61]. The lack of data on behavioral weight loss interventions and cancer events as a study outcome highlights the need for future studies with long-term follow-up to build a comprehensive understanding of the mechanisms underlying cancer risk and other health benefits related to behavioral and surgical weight loss intervention.

As with most systematic reviews, the major limitation centered on the shortcomings of the reviewed literature. Due to the small number of high-quality studies and inconsistent definition of self-reported intentional weight loss and weight cycling, we were not able to perform a quantitative analytical summary for those studies. The inconsistencies prevented us from comparing results across studies. Data on self-reported weight cycling and self-reported intentional weight loss were self-reported and only collected once. Future studies using longitudinal measures and integration of electronic health record that collects standardized weight measures over time are needed. Additionally, none of the bariatric surgery studies provided information on the amount of weight loss. Dichotomizing the exposure as bariatric surgery vs. no surgery treats women within these groups as homogeneous and does not account for variation in the amount of weight reduction in the surgical group. Finally, our quantitative results related to bariatric surgery are only generalizable to that patient population. Demographic and clinical characteristics, including, age, income, obesity severity, and co-existing health conditions, likely differ between surgical and non-surgical weight loss cohorts. Therefore, the interpretation of the results needs to be cautious.

The major strengths of this systematic review include an overall rigorous approach guided by the PRISMA criteria, explicit inclusion criteria, a comprehensive search of several databases, and duplicate reviews of titles/abstracts, full-text, and data to ensure accuracy before analysis. In addition, we assessed the quality of each included study to characterize the available scientific evidence. To our knowledge, this is the first review specifically focused on self-reported weight cycling after intentional weight loss. Our finding of increased endometrial cancer risk among weight cyclers is an important extension of the literature on health outcomes of weight loss. We also updated the synthesis of literature related to bariatric surgery and endometrial cancer risk. Our topic is one of increasing importance given the obesity epidemic, and this review can help identify gaps in research and suggests the area for future research.

CONCLUSIONS

Current evidence from studies assessing intentional weight loss and weight cycling suggest that intentional weight loss is associated with lower endometrial cancer risk and weight cycling is associated with increased risk of endometrial cancer. Our study identified important research gaps which suggest future research to address current limitations. Strategies to improve awareness and maintenance of weight loss among women with obesity are needed to reduce endometrial cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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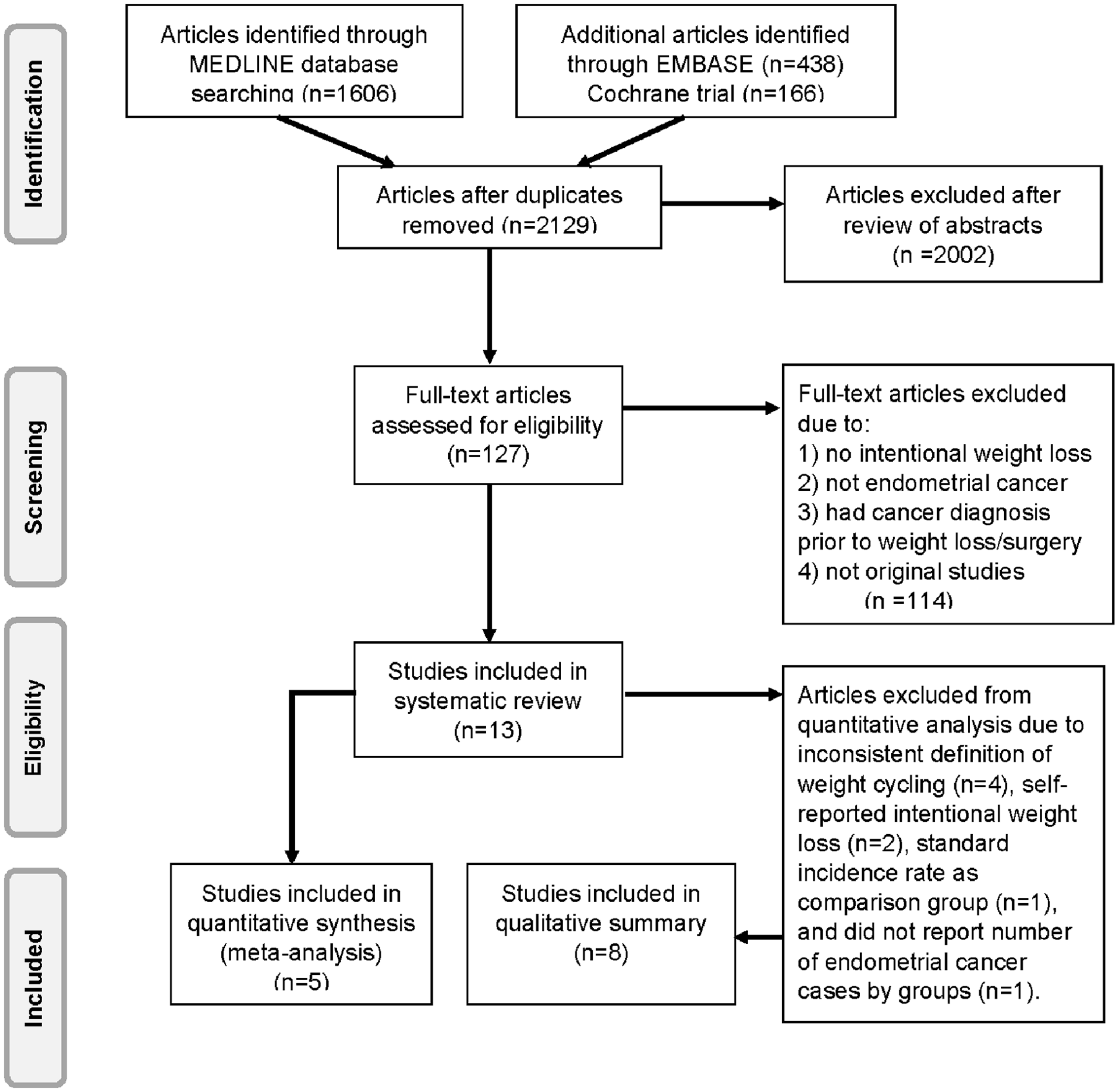

Figure 1.

PRISMA diagram of study identification and selection.

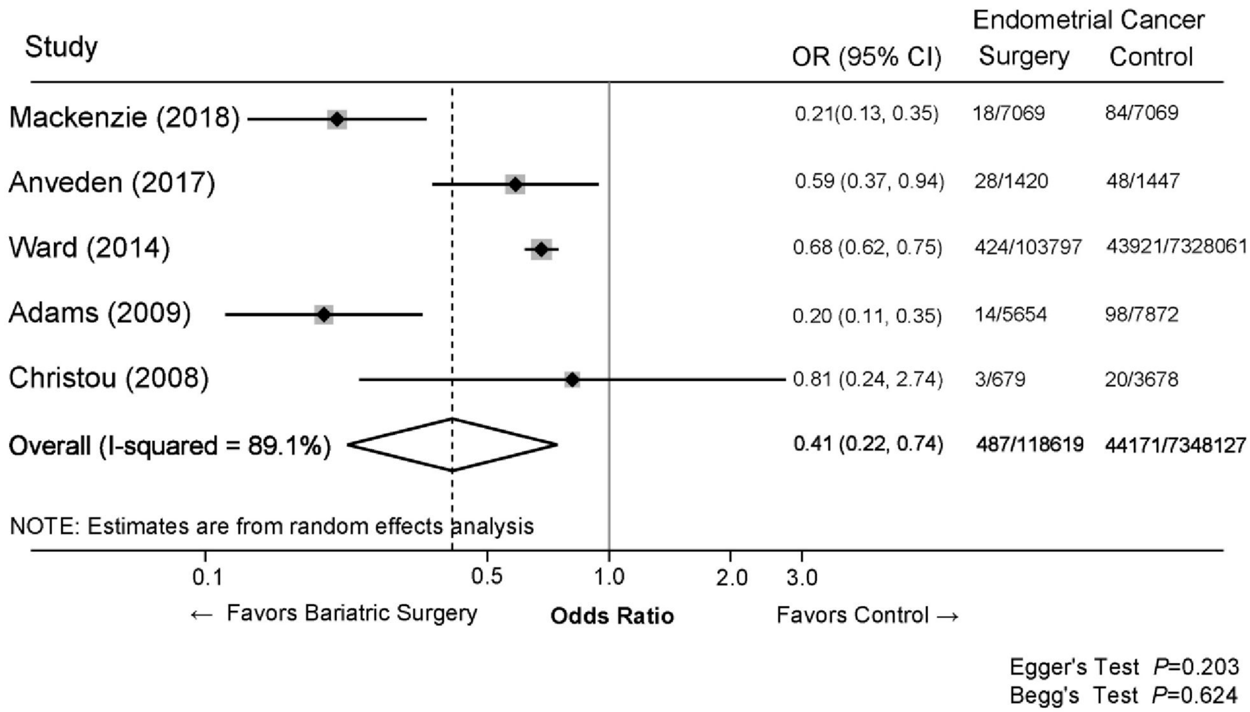

Figure 2.

Meta-analysis of the association between bariatric surgery and the risk of endometrial cancer.

Forest plot of effect estimation (Odds Ratios (OR) and 95% confident interval (95% CI)) comparing endometrial cancer risk between patients had bariatric surgery and patients did not have bariatric surgery (control). The heterogeneity of effect size estimates across studies was assessed by I^2 statistic and the publication bias was assessed by Egger's and Begg's tests.

Table 1a.

Study descriptions of self-reported intentional weight loss, weight cycling, and the risk of endometrial cancer

Author, year	Study type	Population	Study design	Recruitment year	Endometrial cancer diagnosis year	Developed endometrial cancer	Total N	Weight status measures	Weight cycling/weight loss definition
Self-reported intentional weight loss									
Luo, 2017	prospective cohort	WHI (U.S)	WHI cohort without history of cancer, did not have hysterectomy, did not have endometrial cancer diagnosis between baseline and year-3 visit cases: all incident endometrial cancer occurrences diagnosed after the year-3 visit	1993–1998	from the year-3 visit to the first of either an endometrial cancer diagnosis, a date of hysterectomy, a date of death, loss to follow-up, or end of current follow-up (9/30/2015)	566	36793	Measured at baseline and year 3 follow-up	stable weight: within ±10lbs weight gain (≥10 lbs) weight loss (≥10 lbs) intentional; unintentional
Parker, 2003	prospective cohort	Iowa Women's Health study (U.S)	Iowa Women's Health Study randomly selected women between the age 55–69 in January 1986, had a valid driver's license in 1985 cases: endometrial cancer was identified by computer linkage with state health registry of Iowa	1986	1993–2000	142	21707	the 1992 questionnaire	never lost ≥20lbs, intentional loss, unintentional loss, ≥ intentional plus ≥ unintentional
Weight Cycling									
Welti, 2017	cohort	WHI observation (U.S)	WHI observational study, postmenopausal (50–79 yrs), no missing information on weight change, baseline covariates, or reported history of cancers at baseline, or reported hysterectomy at baseline	1993–1998	1994–2014	788	47897	baseline questionnaire	weight cycling: intentional weight loss and subsequent regain; stayed the same (<10lbs); steady gained; lost weight as an adult and kept it off; weight went up and down again ≥10lbs (1–3×, 4–6×, 7–10×, >10×)
Nagle, 2013	population-based case-control	Australia	cases: newly diagnosed, histologically confirmed, epithelial endometrial cancer diagnosed controls: randomly selected from voter system matched by residence state and age + participants from another study	2005–2007	2005–2007	1398	2936	telephone interview/ self-administered questionnaire	weight cycling: never intentionally lost > 9kg and regained within 12 month; lost >9 kg and kept it off; >1× intentionally lost >9 kg and regain within 12 months
Stevens, 2012	prospective cohort	ACS cancer prevention study II nutrition cohort (U.S)	CPS-II Nutrition Cohort (50–74 yrs)	1992/1993	follow-up started in 1997 and every 2 years until the date of endometrial cancer diagnosis,	559	38148	baseline questionnaire	weight cycling was asked "how many times in your life have you purposefully …" weight cycling: # of lost ≥10lbs and regained:

Author, year	Study type	Population	Study design	Recruitment year	Endometrial cancer diagnosis year	Developed endometrial cancer	Total N	Weight status measures	Weight cycling/weight loss definition
					death, date of the last returned survey, or June 30, 2007, whichever came first				non-cycler, 1–4 times, 5–9 times ≥10 times
Trentham-Dietz, 2006	population-based case-control	Wisconsin (U.S)	cases: Wisconsin cancer registry; controls: random selected from population lists of drivers and Medicare beneficiaries, matched by age distribution	1992–1995	cases: 1/1/1991–12/31/1994	740	3082	structured telephone interview	weight cycling: intentionally lost >20lbs and regain more than half within 1 yr, frequency, age at it last happened

Table 1b.

Study descriptions of bariatric surgery and endometrial cancer risk

Author, year	Study type	Population	Study period	Comparison	Developed endometrial cancer	Did not develop endometrial cancer	Total N	Age (mean)	Surgical procedure type
Mackenzie, 2018	retrospective cohort	Hospital Episode Statistics (England)	1997–2012	bariatric surgery vs.	18	7051	7069	42	gastric bypass, gastric banding, and sleeve gastrectomy
				propensity-matched obese individual without surgery	84	6985	7069	42	
Anveden, 2017	prospective cohort	Swedish Obese Subjects Study (Sweden)	1987–2013	bariatric surgery vs.	28	1392	1420	47.2	gastric banding, vertical banded gastroplasty, gastric bypass
				conventional obesity treatment	48	1399	1447	48.8	
Schauer, 2017	retrospective cohort	Kaiser Permanente	2004–2014	bariatric surgery vs.	322	71568	17998	45.0	gastric bypass, sleeve gastrectomy, laproscopic adjustable band, biliopancreatic diversion vertical gastric banding
				obese individual without bariatric surgery			53892	45.1	
Ward, 2014	retrospective cohort	University Health System Consortium (U.S)	2009–2013	bariatric surgery vs.	424	10373	10797	52.6	history of prior bariatric surgery
				obese women with no history of bariatric surgery	43291	7284770	7328061		
Ostlund, 2010	retrospective cohort	Swedish Patient Register (Sweden)	1980–2006	bariatric surgery vs. standardized incidence rate in general population	54	10067	10121	NA	gastric banding, vertical banding gastroplasty, or gastric bypass
Adams, 2009	retrospective cohort	Utah (U.S)	1984–2007	bariatric surgery vs.	14	5640	5654	38.9	roux-en-y gastric bypass
				severe obese adults	98	7774	7872	39.1	
Christou, 2008	retrospective cohort	RAMQ (Canada, McGill University)	1986–2002	bariatric surgery vs.	3	676	679	45.1	roux-en-y isolated gastric bypass, vertical banded gastroplasty, roux-en-y gastric bypass, laparoscopic roux-en-y isolated gastric bypass
				morbidly obese individuals with no history of bariatric surgery	20	3658	3678	46.7	

Table 2.

Qualitative synthesis: self-reported intentional weight loss, weight cycling, and endometrial cancer risk

Author, year	Comparison	Effect estimates	Adjustment
Self-reported intentional weight loss			
Luo, 2017	weight gain vs. stable weight	HR=1.26 (1.00–1.57)	age at enrollment, race/ethnicity, education, smoking pack-years, recreational physical activity, history of hormone therapy use, parity, age of menarche, age at first birth, family history of endometrial cancer, and BMI
	weight loss vs. stable weight	HR=0.70 (0.51–0.98)	
	intentional weight loss vs. stable weight	HR=0.61 (0.40–0.92)	
	unintentional weight loss vs. stable weight	HR=0.91 (0.56–1.46)	
Parker, 2003	weight loss ≥20lbs intentional vs. never lost ≥20lbs	RR=0.96 (0.61–1.52)	age, BMI, BMI^2, waist-to-hip ratio, physical activity, education, marital status, smoking status, pack-years cigarettes, current estrogen use, alcohol use, parity, and multivitamin use
	weight loss ≥20lbs unintentional vs. never lost ≥20lbs	RR=1.29 (0.81–2.05)	
	weight loss ≥20lbs intentional + ≥20lbs unintentional vs. never lost ≥20lbs	RR=1.38 (0.85–2.25)	
Weight cycling			
Welti, 2017	weight gain vs. stable weight	RR=1.16 (0.95–1.42)	age, race/ethnicity, education, income, smoking status, alcohol intake, physical activity, hormone therapy use, health eating index, BMI at baseline
	weight loss vs. stable weight	RR=1.02 (0.62–1.68)	
	weight cycle vs. stable weight	RR=1.23 (1.01–1.49)	
Nagle, 2013	lost and maintained >9kg vs. no intentional weight loss followed by regain	OR=1.02 (0.71–1.45)	age, age at menarche, parity, duration of oral contraceptive pill use, hormone replacement therapy use>3month, smoking status, diabetes, recent BMI
	lost and gained >9kg 1+times vs. no intentional weight loss followed by regain	OR=2.33 (1.58–3.44)	
Stevens, 2012	1–4 times weight cycles vs. non-cycler	RR=1.07 (0.87–1.32)	alcohol use, smoking, physical activity, family history of EC, diabetes, number of live birth/age at first birth, age at menarche, age at menopause, hormone replacement therapy use, oral contraceptive use, and total energy intake, recent BMI
	5–9 times weight cycles vs. non-cycler	RR=1.14 (0.85–1.53)	
	10+ times weight cycles vs. non-cycler	RR=1.05 (0.77–1.42)	
Trentham-Dietz, 2006	ever weight cycling vs. never	OR=1.27 (1.00–1.61)	age, age at menarche, parity, menopausal status, age at menopause, smoking, postmenopausal hormone use, recent BMI, recent physical activity, and diabetes
	once weight cycling vs. never	OR=1.20 (0.84–1.71)	
	2–4 times weight cycling vs. never	OR=1.36 (0.98–1.88)	
	5+ times weight cycling vs. never	OR=1.26 (0.80–1.97)	

HR: Hazard Ratio; RR: Risk Ratio; OR: Odds Ratio; BMI: Body Mass Index

Table 3.

Quality assessment of studies included in the systematic review

	SELECTION				COMPARABILITY	OUTCOME			
Author, year	**Representative-ness of the exposed**	**Selection of the non-exposed**	**Ascertainment of exposure**	**Outcome of interest was not present at start of intervention**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Follow-up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	**TOTAL SCORE**
Self-reported intentional weight loss									
Luo, 2017	1	1	0	1	2	1	1	1	8
Parker, 2003	1	1	0	0	2	1	1	0	6
Weight cycling									
Welti, 2017	1	1	0	1	2	1	0	1	7
Nagle, 2013	1	0	0	1	2	1	0	1	6
Stevens, 2012	1	1	0	1	2	1	0	1	7
Trentham-Dietz, 2006	1	1	1	1	2	1	0	1	8
Bariatric Surgery									
Mackenzie, 2018	1	1	1	1	2	1	1	1	9
Anveden, 2017	1	1	1	1	2	1	1	1	9
Schauer, 2017	1	1	1	0	2	1	1	1	8
Ward 2014	1	1	1	0	1	1	0	1	6
Ostlund, 2010	1	0	1	1	1	1	0	1	6
Adams, 2009	1	1	1	1	2	1	0	1	8
Christou, 2008	1	1	1	1	2	1	1	1	9