Obesity and Endometrial Cancer

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Abstract:

Endometrial cancer is the sixth most common cancer in women worldwide and the most common gynecologic malignancy in the developed world. This chapter explores the current epidemiologic evidence on the association between obesity and endometrial cancer risk and mortality. Using body mass index (BMI) as a measure of obesity, we found that obesity (defined as BMI > 30 and < 35 kg/m^2) was associated with a 2.6-fold increase in endometrial cancer risk, while severe obesity (BMI > 35 kg/m^2) was associated with a 4.7-fold increase compared to normal-weight women (BMI < 25 kg/m^2). Increased central adiposity also increased endometrial cancer risk by 1.5- to twofold. Among both healthy and endometrial cancer patient populations, obesity was associated with a roughly twofold increase in endometrial cancer-specific mortality. This risk reduction was also observed for obesity and all-cause mortality among endometrial cancer patients. In the few studies that assessed risk associated with weight change, an increased endometrial cancer risk with weight gain and weight cycling was observed, whereas some evidence for a protective effect of weight loss was found. Furthermore, early-life obesity was associated with a moderately increased risk of endometrial cancer later in life. There are several mechanisms whereby obesity is hypothesized to increase endometrial cancer risk, including increased endogenous sex steroid hormones, insulin resistance, chronic inflammation and adipokines. Further research should focus on histological subtypes or molecular phenotypes of endometrial tumors and population subgroups that could be at an increased risk of obesity-associated endometrial cancer. Additionally, studies on weight gain, loss or cycling and weight loss interventions can provide mechanistic insight into the obesity–endometrial cancer association. Sufficient evidence exists to recommend avoiding obesity to reduce endometrial cancer risk.

Keywords: Endometrial cancer | Obesity | Incidence | Survival | Biomechanisms

Book chapter:

1 Basic Epidemiology of Endometrial Cancer

1.1 Incidence Rates

Endometrial cancer is the sixth most common cancer in women worldwide, with an estimated 320,000 incident cases in 2012 [1]. In the United States (U.S.), it is the fourth most common cancer in women and the most common gynecologic malignancy diagnosed, with an estimated 49,154 incident cases of uterine cancer in 2012 [2].

Endometrial cancers can be divided into two histological subtypes [3]. Type I endometrial cancers are estrogen-driven and have endometrioid differentiation, while Type II endometrial cancers are not estrogen-dependent and are classified as non-endometrioid (serous, clear cell, mucinous) [4]. Type I endometrial cancers represent approximately 70–80 % of all endometrial cancers [5] and tend to have a more favorable prognosis than Type II cancers, which are usually more aggressive and consequently associated with poorer prognosis [6].

Worldwide incidence rates of endometrial cancer have been increasing, particularly in the twenty-first century, where age-standardized incidence rates have increased from 6.5 per 100,000 in 2002 [7] to 8.2 per 100,000 in 2012 [1]. Furthermore, Type I endometrial cancers have been increasing in the U.S. and in Europe [8, 9, 10]. This increased incidence of endometrial cancer can likely be attributed to changes in lifestyle risk factors (e.g., diet, sedentary behavior and use of hormone replacement therapy), which are all strongly associated with endometrial cancer risk [8, 11].

1.2 Mortality Rates

An estimated 76,000 endometrial cancer deaths occurred worldwide in 2012 [1]. The five-year survival rates for endometrial cancer are relatively high and estimated to be 82 % in the U.S. [12]. Given the better cancer screening and treatment programs, mortality rates for endometrial cancer are lower in developed countries compared to developing countries [7]. Survival rates for endometrial cancer increase with earlier diagnosis [13].

1.3 Major Risk Factors

Risk of endometrial cancer increases with age, and most cases are diagnosed postmenopause [5]. Endometrial cancers diagnosed in older women tend to be of higher grade and stage compared to younger women [14]. In the U.S., incidence rates are higher in white women compared to other ethnic groups, while mortality is significantly worse in black women compared to white women [15, 16]. Other risk factors for endometrial cancer risk include long-term exposure to unopposed estrogens, high postmenopausal concentrations of estrogens, nulliparity, history of breast cancer and first-degree family history of endometrial cancer [5, 17]. Among endometrial cancer patients, risk factors for endometrial cancer mortality (all-cause or endometrial cancer-specific) include prediagnosis obesity, type 2 diabetes mellitus and heart disease [18, 19, 20, 21]. The World Cancer Research Fund Continuous Update Project panel has deemed there to be *convincing* evidence for the association between body fatness and increased risk of endometrial cancer [22]. Obesity ranks among the strongest risk factors for endometrial cancer development [11], and it is strongly hypothesized that the increasing global prevalence of obesity, particularly in developed countries, is contributing to the overall increase in endometrial cancer incidence [11, 23]. The purpose of this chapter is to provide an updated review of the

extant literature on obesity and endometrial cancer and to highlight the current gaps in the epidemiologic evidence.

2 Literature Review Methods

A search for studies of endometrial cancer incidence and mortality related to obesity was performed using PubMed to search the MEDLINE database. Search terms used to identify obesity were "body mass index," "BMI," "waist circumference," "hip circumference," "waist-to-hip ratio," "body weight," "obesity," "adiposity" and "anthropometry," along with "endometrial cancer" and "endometrial neoplasms" as search terms to indicate endometrial cancer. The search was not restricted by date, but only included studies in English up to March 2016. Overall, 38 cohort studies and 42 case–control studies investigating obesity and endometrial cancer risk were identified, with three pooled studies from the Epidemiology of Endometrial Cancer Consortium (E2C2) [24], an NCI-supported consortium consisting of over 45 studies worldwide. Twelve studies investigating obesity and endometrial cancer mortality in both healthy and endometrial cancer patient populations were identified using the above search terms along with "survival," "mortality" and "death."

Studies were excluded if no point estimates and 95 % confidence intervals (CIs) were provided for risk and mortality estimates ($n = 6$ excluded). For studies with multiple publications, the most recent update or largest sample size publications were selected for this review ($n = 9$ excluded). To provide more uniform assessments of endometrial cancer risk and mortality, only studies presenting estimates for categorical adiposity measurements were included ($n = 10$ excluded). An additional three studies were identified that investigated obesity and mortality, but were not included because of limited event observations (<20 deaths) [25, 26, 27]. This additional exclusion resulted in 28 cohort studies, 29 case–control studies and one pooled study for inclusion in this review for endometrial cancer incidence. There were three studies [28, 29, 30] that investigated obesity and endometrial cancer-specific mortality in healthy populations and three studies [18, 31, 32] for endometrial cancer-specific or all-cause mortality in endometrial cancer patient populations.

In addition, studies that presented risk estimates stratified by other variables were pooled in order to obtain one representative estimate for each study. Since BMI categorization varied across studies, risk estimates were separated into obesity (class I—generally BMI ≥ 30 or $30 \leq \text{BMI} < 35$) and severe obesity (class II or III—generally BMI ≥ 35). Random-effect models were used to calculate pooled estimates with 95 % CIs for each set of studies [33].

3 Obesity and Endometrial Cancer Risk

3.1 BMI and Risk

There were 25 cohort studies, 28 case–control studies and one pooled study from the E2C2 investigating the relation between BMI and endometrial cancer risk identified, with almost all studies showing a statistically significant positive association. Using data from 26 case–control studies [34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59], the effect estimates of obesity ($30 < \text{BMI} < 35$) and endometrial cancer risk ranged

from 1.00 (95 % CI 0.60–1.50) [40] to 9.18 (95 % CI 4.30–19.62) [34] (Fig. 1). The overall pooled risk estimate for endometrial cancer risk associated with obesity for case–control studies was 2.32 (95 % CI 2.08–2.58), compared to normal-weight individuals (generally BMI < 25). Similarly, 25 cohort studies [17, 28, 29, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81] ranged in effect estimates from 1.50 (95 % CI 1.10–2.10) [63] to 4.50 (95 % CI 2.62–7.72) [17], resulting in an overall pooled estimate of 2.49 (95 % CI 2.28–2.73), compared to normal-weight individuals (generally BMI < 25). The pooled study from the E2C2 reported an effect estimate of 2.11 (95 % CI 1.46–3.05) [24], and the overall pooled estimate for obesity and endometrial cancer risk was 2.65 (95 % CI 2.43–2.90).

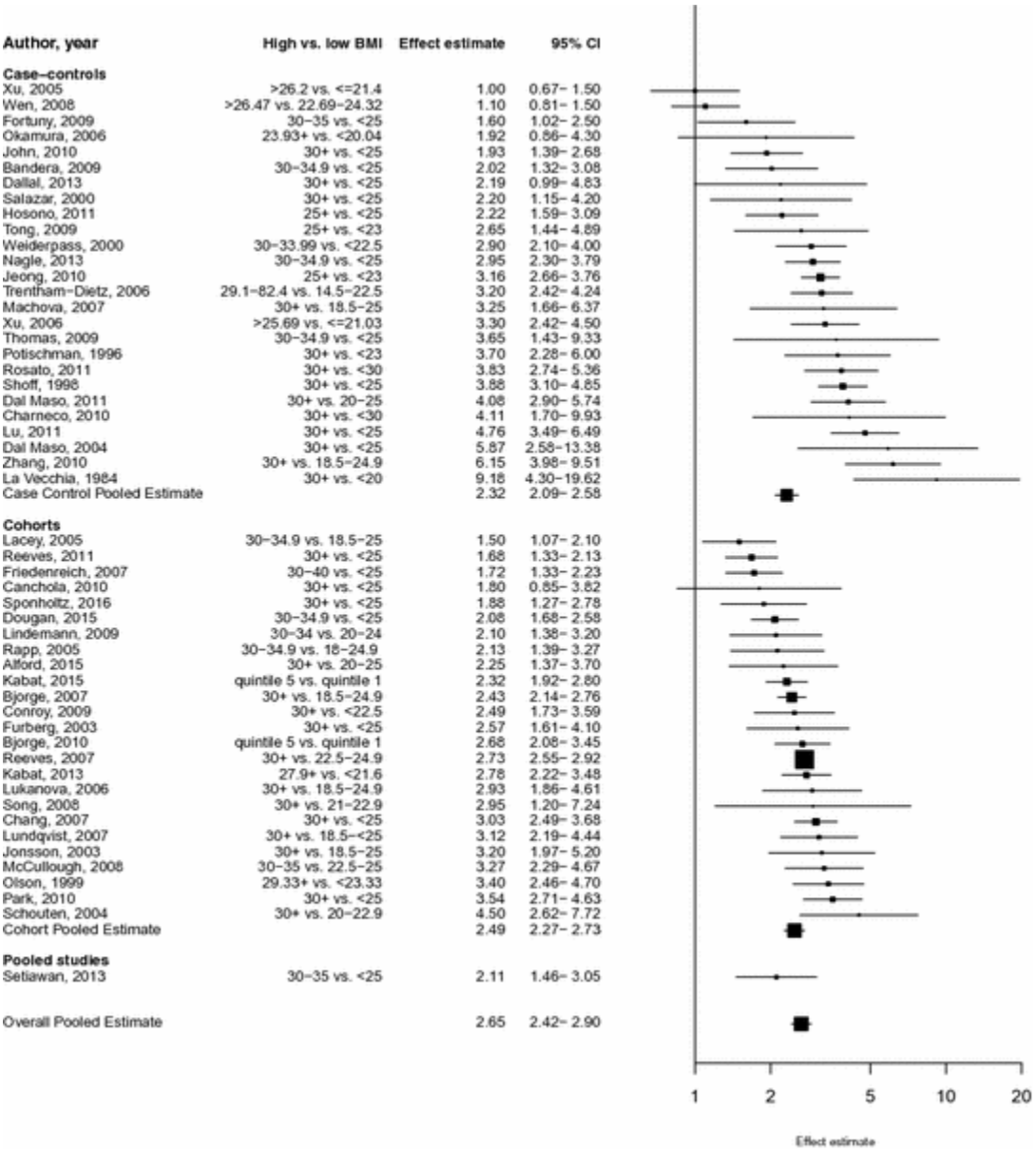

Fig. 1. Case–control and cohort studies of obese BMI and endometrial cancer risk

Effect estimates for endometrial cancer risk in relation to severe obesity were notably higher than associations with obesity (Fig. 2). Seven case–control studies [38, 46, 47, 48, 59, 82, 83] and

seven cohort studies [63, 64, 68, 70, 73, 79, 81] investigated this relation, resulting in pooled estimates of 6.45 (95 % CI 4.98–8.35) and 3.61 (95 % CI 2.85–4.58), respectively. Additionally, the pooled study from the E2C2 reported an estimate of 4.80 (95 % CI 2.13–10.82) [24]. The overall pooled estimate for severe obesity and endometrial cancer risk was 4.66 (95 % CI 3.78–5.75).

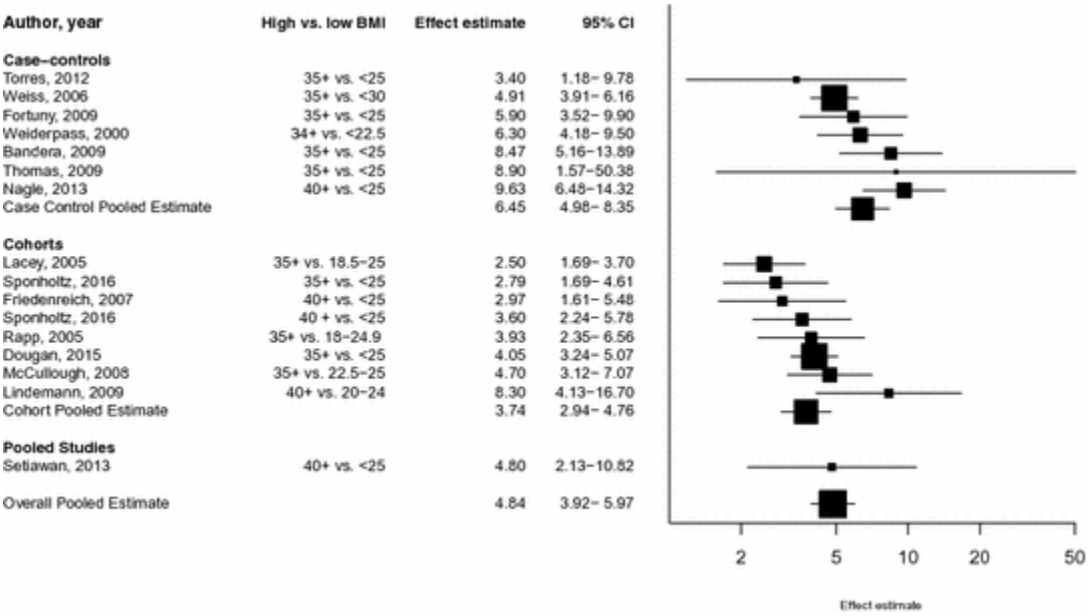

Fig. 2. Case–control and cohort studies of severely obese BMI and endometrial cancer risk

3.2 Central Adiposity and Risk

Recently, central adiposity measures, defined either as waist circumference or as waist-to-hip ratio, have also been considered in etiologic studies of anthropometry and endometrial cancer risk. To date, five case–control [40, 45, 54, 57, 84] and five cohort studies [68, 72, 74, 80, 81] examining waist circumference showed statistically significant pooled estimates of 2.30 (95 % CI 1.71–3.09) and 1.58 (95 % CI 1.18–2.12), respectively, for higher waist circumference (generally >90 cm) and endometrial cancer risk (Fig. 3). The overall pooled estimate for all studies combined was 1.92 (95 % CI 1.57–2.35). Although the strength of association was weaker, higher waist-to-hip ratio (generally >0.85) was also associated with an increased risk of endometrial cancer risk. Three of the five case–control studies that examined waist circumference and endometrial cancer risk also considered waist-to-hip ratio, and their pooled estimate was 1.78 (95 % CI 1.24–2.55) [40, 45, 54]. All five cohort studies that measured the effect of waist circumference on endometrial cancer risk also measured waist-to-hip ratio, along with one additional study [68, 72, 74, 76, 80, 81]. The pooled estimate for waist-to-hip ratio on endometrial cancer risk was 1.29 (95 % CI 1.13–1.47). The overall pooled estimate for higher waist-to-hip ratio and risk of endometrial cancer was 1.43 (95 % CI 1.33–1.54) from these nine studies.

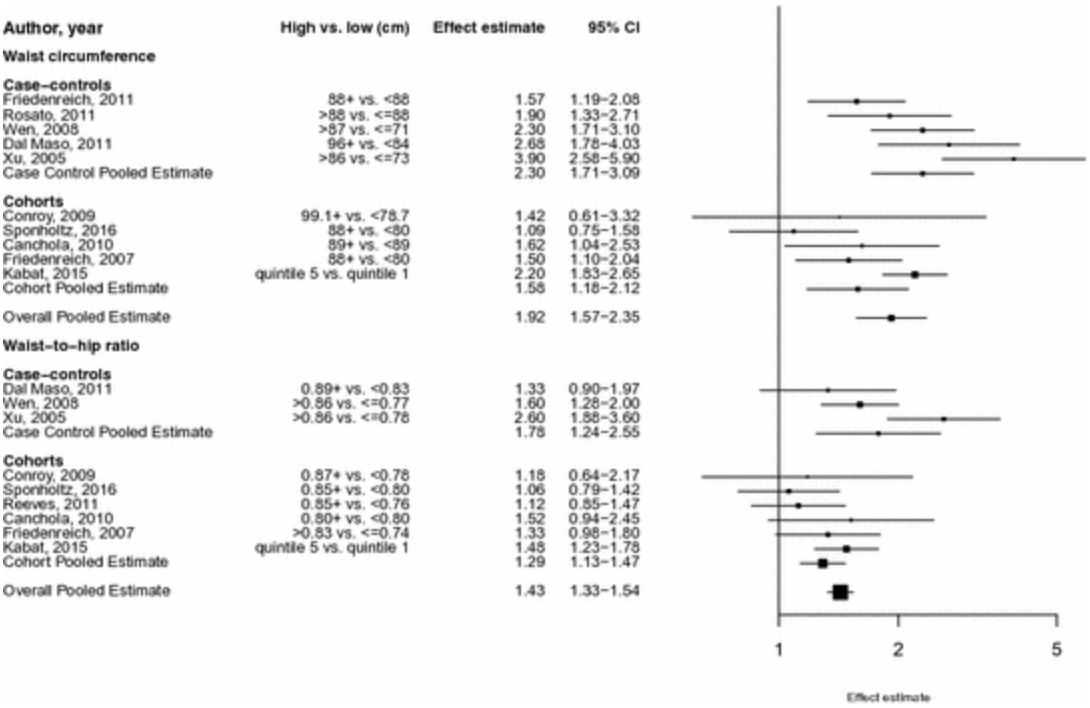

Fig. 3. Central adiposity and endometrial cancer risk

3.3 Weight Change (Gain/Loss), Weight Cycling and Risk

To date, 17 studies have investigated the effect of weight change (gain or loss) on the risk of endometrial cancer (Fig. 4). In general, weight gain was significantly associated with an increased risk of endometrial cancer in both case–control [38, 42, 43, 48, 55, 56, 59] and cohort [17, 27, 62, 67, 68, 74, 75, 79, 81, 85] studies. There was considerable heterogeneity between studies with respect to weight gain measurement, and thus, pooled estimates are not presented. Most studies examined weight gain from early adulthood (age 18–25 years) and found that weight gain of roughly 20 kg was associated with an approximately twofold increase in endometrial cancer risk.

Studies in weight loss [42, 74, 79, 85] trended toward a protective effect on endometrial cancer risk, although this effect was statistically significant in only one study [79]. Similar to studies of weight gain, studies on weight loss were heterogeneous in measurements of weight loss, which precluded comparing the estimates or pooling them. Lastly, only three studies [42, 59, 86] investigated the role of weight cycling (purposeful loss of weight, followed by weight gain). All studies indicated an increased risk of endometrial cancer with weight cycling; two of these studies were statistically significant [42, 59]. In these studies, odds ratios for ever versus never experiencing weight cycling over lifetime ranged from 1.27 (95 % CI 1.00–1.61) [42] to 2.30 (95 % CI 1.54–3.43). Additionally, an increased number of weight cycles appeared to attenuate the risk as these estimates were statistically nonsignificant [42, 86].

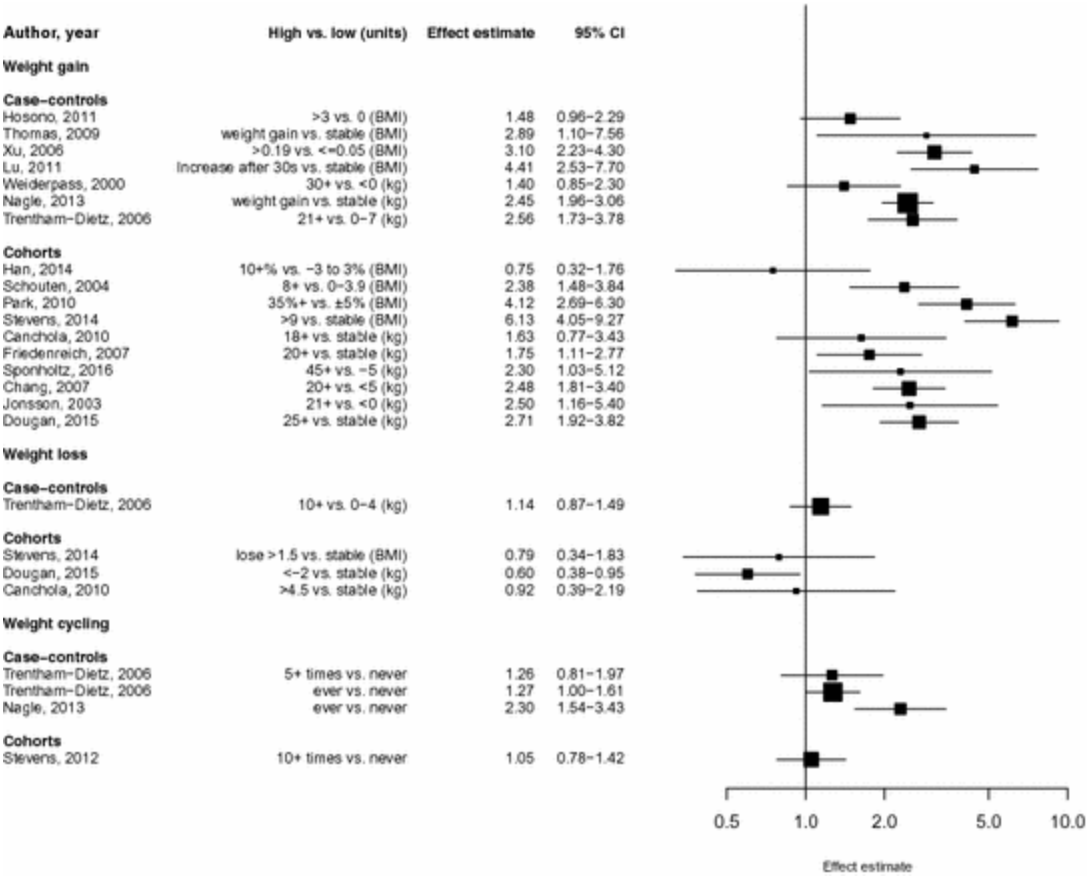

Fig. 4. Weight change (gain and loss), weight cycling and endometrial cancer risk

3.4 Childhood/Adolescence and Early Adult Weight and Risk

The role of childhood/adolescence or early adulthood obesity on endometrial cancer risk later in life was examined in 14 studies [17, 38, 43, 48, 54, 55, 59, 67, 74, 75, 79, 81, 85, 87] (Fig. 5). Early adulthood obesity increased endometrial cancer risk by 33 % (95 % CI 0.94–1.88) for case–control studies [38, 43, 48, 55, 59] and by 57 % (95 % CI 1.38–1.79) for cohort studies [17, 67, 74, 75, 79, 81, 85] compared with normal weight in early adulthood. The overall pooled estimate for early adulthood obesity and endometrial cancer risk was 1.44 (95 % CI 1.22–1.70). Similarly, increased endometrial cancer risk associated with childhood/adolescent obesity was smaller in magnitude for case–control studies [43, 54] and very close to the null for cohort studies [79, 88]. These risk estimates must be interpreted with caution since accurate exposure measurements for early adulthood or childhood/adolescent obesity were often not available for these studies. BMI reporting tended to rely on the participants' ability to recall their early-life anthropometry, and thus, measurement error likely affected these results.

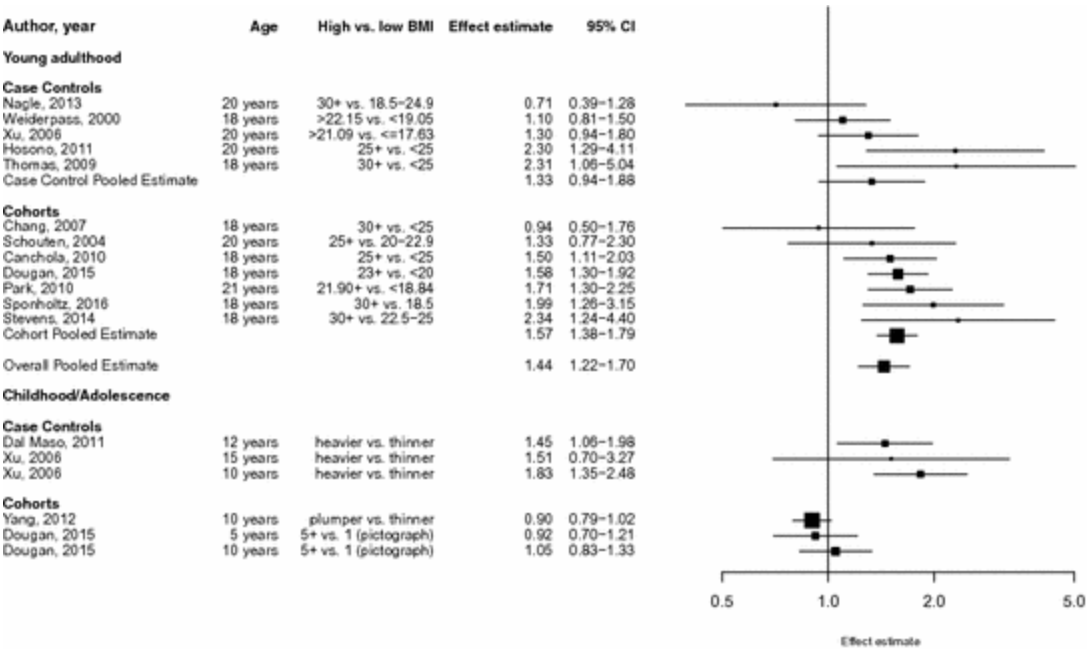

Fig. 5. Childhood/adolescence and early adult weight and endometrial cancer risk

4 Obesity and Endometrial Cancer Survival

4.1 Weight/BMI and Survival

Only six studies have investigated the association between BMI and mortality (all-cause or endometrial cancer-specific) among healthy or endometrial cancer patient populations (Fig. 6). With respect to endometrial cancer-specific mortality, there were six studies with effect estimates for the association with obesity [18, 29, 30, 31, 32, 66], three of which were in healthy populations [28, 29, 30]. All point estimates were above the null value, resulting in a pooled estimate of 2.39 (95 % CI 2.04–2.80) in healthy populations and 1.91 (95 % CI 1.29–2.82) in endometrial cancer patient populations. Severe obesity was also significantly associated with endometrial cancer-specific mortality among healthy populations [28, 30], with a pooled estimate of 4.69 (95 % CI 2.68–8.22), as well as among endometrial cancer patients [31, 32], with a pooled estimate of 1.96 (95 % CI 1.25–3.07). Of the three studies that examined the association between obesity and all-cause mortality in endometrial cancer patient populations [18, 31, 32], all observed a positive association, with a pooled estimate of 1.64 (95 % CI 1.29–2.09). Two of these studies also analyzed the association between severe obesity and all-cause mortality [31, 32], and both reported statistically significant positive associations, with a pooled estimate of 2.06 (95 % CI 1.55–2.74).

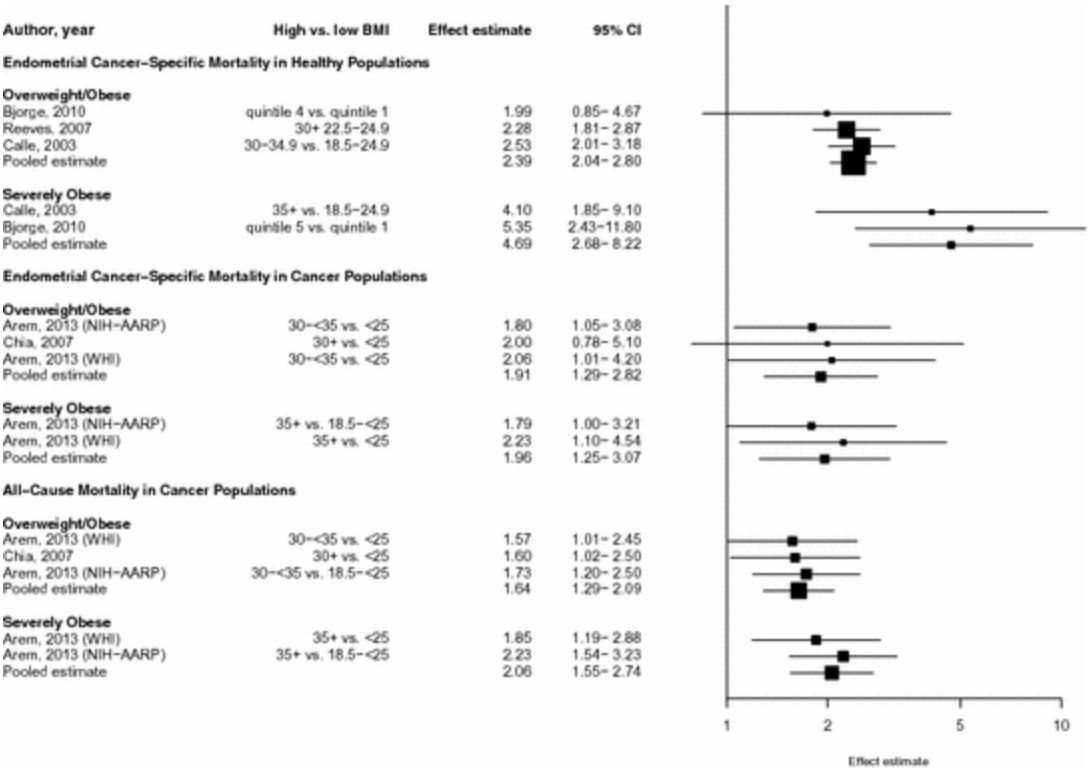

Fig. 6. Obesity (BMI) and all-cause or endometrial cancer-specific mortality

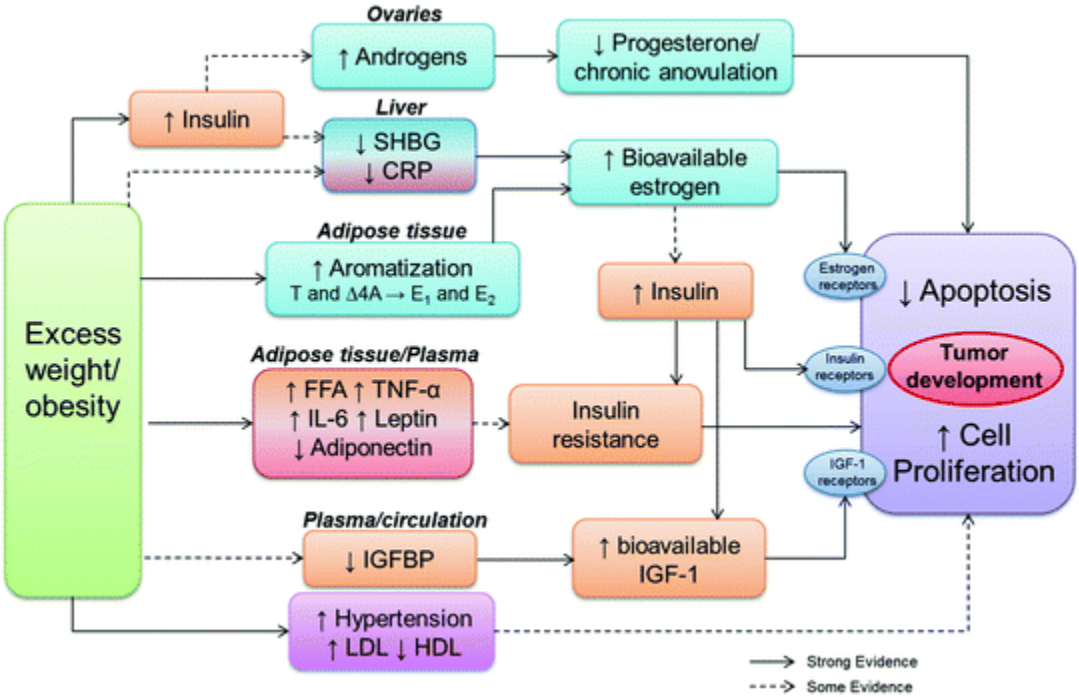

Fig. 7. Hypothesized biologic pathways relating excess obesity to endometrial cancer risk. *Note* *Δ4A* androstenedione; *CRP* C-reactive protein; *E1* estrone; *E2* estradiol; *FFA* free fatty acids; *HDL* high-density lipoprotein; *IGFBP* insulin growth factor binding protein; *IGF-1* insulin-like growth factor-1; *IL-6* interleukin-6; *LDL* low-density lipoprotein; *SHBG* sex-hormone-binding protein; *T* testosterone; *TNF-α* tumor necrosis factor-α

5 Biologic Mechanisms Involved in the Association of Obesity and Endometrial Cancer Risk and Survival

Given the strong associations between obesity and increased endometrial cancer risk and mortality, elucidating the mechanisms whereby this association occurs can improve our understanding of the etiology of this disease and aid in developing more efficient strategies for cancer prevention. There are several proposed mechanisms whereby obesity can lead to endometrial carcinogenesis (Fig. 7) [88, 89]. These include pathways involving endogenous sex steroid hormones, insulin resistance and inflammation.

5.1 Endogenous Sex Steroid Hormones

The "unopposed estrogen" theory suggests that endometrial cancer risk is increased in women with high plasma levels of bioavailable estrogen, or low plasma levels of progesterone [90]. These altered sex steroid hormone levels have been associated with Type I endometrial carcinomas [91]. Exposure of the endometrium to estrogen when unopposed by progesterone stimulates endometrial cell growth and proliferation, thus increasing the likelihood of malignant cell development [92]. Bioavailable estrogen increases IGF-1 receptor levels and reduces insulin growth factor binding protein (IGFBP) levels, thus increasing the affinity of IGF-1 with its receptor within endometrial tissues [93]. Conversely, progesterone down-regulates estrogen receptors, stimulates the synthesis of IGFBP-1, reduces inflammation and promotes cell differentiation and apoptosis within the endometrium [88, 92, 94].

Several case–control studies have reported increased total [35, 95, 96, 97, 98] and bioavailable [35, 97] estrogen levels and decreased plasma SHBG levels [35, 98] in postmenopausal women with endometrial cancer compared to controls. One prospective cohort study [99] also reported an increased risk of endometrial cancer risk among postmenopausal women in the top tertile for levels of free estradiol compared to the lowest tertile. Therefore, increases in the synthesis of endogenous estrogen by adipose tissue, coupled with decreased SHBG production by the liver, leads to increased plasma levels of bioavailable estrogen, thereby increasing endometrial cancer risk in obese postmenopausal women [90, 100]. On the other hand, excess weight does not appear to be related to increased bioavailable estrogen levels in premenopausal women with normal androgen levels [101]. Instead, excess weight has been suggested to cause chronic anovulation and reduce progesterone synthesis in premenopausal women, which may then increase bioavailable estrogen levels and the risk of endometrial cancer [90, 99].

Similar to estrogen levels, free testosterone levels were 79 % greater in postmenopausal women with excess weight (BMI $\geq$ 30 kg/m^2) compared to women with a BMI of $\leq$22 kg/m^2 [102]. Increased levels of circulating androgens have also been associated with an increased Type I endometrial cancer risk in both pre- and postmenopausal women [95, 103, 104]. While androgens do not have a direct effect on endometrial cell proliferation, increased levels of androgens are converted into bioavailable estrogen through aromatization within endometrial and adipose tissues [89]. In premenopausal women, chronic anovulation and decreased progesterone levels may occur because of greater androgen production/conversion of androgens to estrogens [90].

Studies in women with polycystic ovarian syndrome (PCOS), a metabolic condition characterized by increased androgen levels, chronic anovulation and insulin resistance [105], have provided some causal evidence between obesity, endogenous sex steroid hormones and endometrial cancer. Two cohort studies have demonstrated an increased risk of endometrial cancer in women with PCOS [105, 106]. Furthermore, weight loss in obese women with PCOS has resulted in normalization of androgen levels and ovulatory cycles [107, 108]. Thus, suggesting a reduction in adipose tissue may decrease the risk of endometrial cancer through reductions in adipose-derived sex steroid hormones.

Taken together, endometrial cancer risk may be increased in women with excess weight directly as a result of greater levels of bioavailable estrogen and lower plasma SHBG levels, as well as indirectly through increased androgen levels. More specifically to premenopausal women, greater estrogen and androgen levels may lead to increased endometrial cancer cell proliferation as a result of reduced progesterone levels and/or chronic anovulation.

5.2 Insulin Resistance

Obesity is associated with chronically increased insulin levels and IGF-1 activity, mechanisms that directly promote cell proliferation and inhibit apoptosis within the endometrium in pre- and postmenopausal women [88, 89]. More specifically, insulin promotes tumor growth by binding to IGF-1 and insulin receptors within the endometrium [109] and has been previously associated with faster endometrial cancer progression [110]. Glucose may also contribute to tumor growth by providing an energy source to cancer cells [111]. Insulin down-regulates IGFBP-1 activity, leading to an increase in bioavailable IGF-1 levels [112]. However, progesterone can counteract these effects by stimulating the production of IGFBP-1, the most abundant IGFBP located in endometrial tissue, thus reducing the quantity of bioavailable IGF-1 [89]. Excess adiposity can ultimately lead to the development of insulin resistance and type 2 diabetes, as a result of chronically increased release of free fatty acids (FFA) into the plasma by adipose tissue [113]. These increased levels of circulating FFA will promote their uptake and oxidation by hepatic and muscle tissues, therefore limiting the use of glucose as a source of energy [113].

Case–control studies reported that significantly more endometrial cancer cases had elevated homeostatic model assessment of insulin resistance (HOMA-IR) scores, which are indicative of insulin resistance, risk of type 2 diabetes, greater IGF-1, insulin and glucose levels compared to controls [114, 115]. Similarly, women within the highest quartile of fasting insulin [116] and HOMA-IR scores [115] had a greater than twofold increase in risk of endometrial cancer compared to women in the lowest quartile, independent of anthropometry measures (e.g., BMI and waist-to-hip ratio). Type 2 diabetes and insulin resistance have been consistently associated with an increased risk of endometrial cancer in meta-analyses [38, 117, 118, 119, 120, 121, 122, 123, 124]. Some studies reported attenuations in the strength of the associations between type 2 diabetes and/or insulin resistance with endometrial cancer risk after controlling for BMI [119, 120], while others did not [38, 117, 118, 122]. These results suggest that the associations between type 2 diabetes/insulin resistance and endometrial cancer risk may be partially explained by BMI [120]. It is also possible that the combination of excess weight and diabetes/insulin resistance may lead to even greater risks of endometrial carcinogenesis [118] as a result of

interactions between increased insulin levels with other adiposity-related biologic mechanisms, such as chronic inflammation or increased estrogen production in postmenopausal women [116]. Finally, it is well known that modest weight loss of 5–10 % can reduce serum glucose levels, improve insulin sensitivity/reverse insulin resistance and decrease IGF-1 levels [125, 126]. Therefore, weight loss may be an efficient strategy for endometrial cancer prevention, as it would contribute to reducing adiposity levels and IGF-1 levels, as well as potentially reversing insulin resistance.

Insulin also indirectly stimulates endometrial carcinogenesis by increasing androgen production within the ovaries, which can lead to chronic anovulation and progesterone deficiencies, as well as decrease the synthesis of SHBG by the liver. Consequently, increased levels of bioavailable estrogens can be diffused into the endometrium [89, 127]. Indeed, Goodman-Gruen and Barrett-Connor [128] reported that postmenopausal women with impaired glucose tolerance or type 2 diabetes had greater levels of total and bioavailable estradiol compared to postmenopausal women with normal glucose tolerance, independent of age and BMI. Decreases in SHBG production by the liver in response to greater insulin levels are proposed to cause this increase in estrogen levels in women with type 2 diabetes [122].

In summary, greater endometrial cancer risk has been consistently associated with increased insulin levels, the presence of insulin resistance and type 2 diabetes. There is also sufficient evidence to suggest direct and indirect associations of endometrial cancer with increased insulin and IGF-1 levels, with amplification of these associations in the presence of obesity.

5.3 Adipokines and Inflammation

A variety of pro- (e.g., tumor necrosis factor (TNF)-α, leptin, interleukin (IL)-6, C-reactive protein (CRP)) and anti- (e.g., adiponectin) inflammatory cytokines, known as adipokines, are secreted by adipose tissue [88, 129, 130]. Obesity is known to increase the release of pro-inflammatory markers, such as TNF-α and IL-6 [131], while decreasing the release of anti-inflammatory markers and promoting a chronic low-grade inflammatory state [132]. IL-6, in turn, stimulates the production and release of CRP by the liver [133].

Chronic, low-grade inflammation has been hypothesized to increase the risk of endometrial cancer by promoting cell proliferation and the production of free radicals that cause DNA damage [134]. Inflammatory markers can also indirectly influence endometrial cancer risk by promoting insulin resistance, hyperglycemia or aromatization activity within adipose tissue and the endometrium [112, 132, 135, 136]. Leptin, a prominent adipokine, stimulates the production and release of IL-6, TNF-α and FFA and also reduces tissue sensitivity to insulin and promotes aromatase activity [137, 138]. Conversely, adiponectin reduces circulating blood glucose and insulin levels, counteracts the pro-inflammatory effects of other cytokines (e.g., TNF-α, IL-6 and CRP), increases tissue sensitivity to insulin and promotes FFA oxidation [139, 140, 141, 142]. Leptin will also directly promote cell growth, whereas adiponectin suppresses cell proliferation within the endometrium [143, 144]. Therefore, a greater leptin/adiponectin ratio is associated with increased endometrial cancer risk [145] and has been shown to be a surrogate marker of insulin resistance in diabetic and non-diabetic individuals [146].

Dossus et al. [132] noted positive and significant associations between CRP and IL-6 with endometrial cancer risk; however, these associations became non-statistically significant after controlling for BMI. Friedenreich et al. [131] added to these findings by reporting statistically significant positive associations between levels of TNF-α, IL-6 and CRP with endometrial cancer risk in the age-adjusted model, but only CRP remained significantly associated with endometrial cancer risk in the multivariable model (i.e., following adjustments for BMI, age and menopausal status among other risk factors). Similar results were found in a case–control study in which a significant positive association between CRP, but not IL-6 and TNF-α, and endometrial cancer risk after adjusting for BMI was observed [147]. Several case–control studies also reported greater levels of serum leptin, lower levels of serum adiponectin and/or greater leptin/adiponectin ratio in cases versus controls [39, 58, 129, 131, 145, 148, 149, 150, 151, 152]. These differences in leptin and adiponectin levels, or the leptin/adiponectin ratio, remained after controlling for BMI [39, 129, 149] and/or other covariates (e.g., age, diabetes and hypertension) [58, 131, 145, 148, 151, 152].

Some studies have reported possible effect modification by BMI when assessing the association between adipokine and endometrial cancer risk [129, 131]. More specifically, Cust et al. [129] reported a stronger inverse association between adiponectin levels and endometrial cancer risk in obese women. In addition, Friedenreich et al. [131] reported significant positive associations between endometrial cancer risk and CRP in women with a BMI of ≥30 kg/m^2, whereas IL-6 was significantly associated with endometrial cancer risk in women with a BMI of ≤25 kg/m^2. Finally, significant decreases in a number of pro-inflammatory adipokines (e.g., IL-6 and TNF-α) coupled with increases in adiponectin levels following an approximate 10 % weight loss [130, 153] suggest that moderate weight loss may reduce the risk of endometrial cancer development through reductions in adipokine levels.

In summary, greater endometrial cancer risk has been associated with an increased low-grade, pro-inflammatory state induced by excess adiposity. There is also evidence to suggest that the overall adipokine–endometrial cancer risk association is independent of BMI and other risk factors (e.g., diabetes, hypertension and estradiol levels), but that the link between specific adipokines with endometrial cancer may also be modified by BMI.

5.4 Metabolic Syndrome

Metabolic syndrome encompasses a number of risk factors/conditions that can increase the risk of metabolic complications, such as type 2 diabetes, cardiovascular disease and cancer [154]. These risk factors include: (1) obesity/excess central adiposity/high waist circumference, (2) hypertension, (3) elevated blood glucose levels/insulin resistance, (4) elevated triglyceride levels and (5) low high-density lipoprotein (HDL) cholesterol levels [154].

A few case–control studies reported significantly greater risk of endometrial cancer in study participants diagnosed with the metabolic syndrome [28, 57, 84], in addition to those presenting individual components of the metabolic syndrome [50, 84, 155]. More specifically, an increased risk of endometrial cancer was noted in individuals with hypertension [28, 50, 58, 84, 151, 155, 156], impaired fasting glucose/insulin resistance [28, 58, 84, 129, 151, 155], obesity/high waist circumference [28, 84, 155] and high triglyceride levels [28, 129, 155, 157]. The risk of

endometrial cancer was also inversely associated with HDL cholesterol levels [129]. Conversely, both no association [129, 157] and an inverse association [158] were reported between total serum cholesterol and/or low-density lipoprotein (LDL) levels with endometrial cancer risk. It has been hypothesized that this lack of, or reverse, association between cholesterol, LDL and endometrial cancer risk may be explained by an increase in bioavailable estrogens [157, 158]. Indeed, Wallace et al. [159] observed lower total cholesterol and LDL levels in menopausal estrogen users, compared to nonusers. Lastly, some studies reported an increased endometrial cancer risk with each additional metabolic syndrome component [28, 57, 129].

Many [28, 129, 151, 155, 156], but not all [157] studies reported that the associations between each metabolic syndrome component and endometrial cancer risk were independent of BMI. Furthermore, the associations between metabolic syndrome components and endometrial cancer risk were strongest for overweight versus normal-weight women [61, 84, 129]. Thus, it is hypothesized that some of the effects of the metabolic syndrome on endometrial cancer risk may be mediated by the presence of obesity/excess weight. In fact, weight loss of approximately 10 % led to reductions in a number of metabolic syndrome components (fasting blood glucose, total cholesterol, triglycerides and LDL levels) [130].

Taken together, the presence of the metabolic syndrome increases the risk of developing endometrial cancer. The presence of excess adiposity and diabetes that often accompany metabolic syndrome provides evidence for the increased risk of endometrial carcinogenesis as a result of greater bioavailable estrogens and circulating insulin/insulin resistance.

5.5 Mechanisms Related to Survival

There is limited evidence regarding the biomechanisms involved in the association between obesity and endometrial cancer survival [31, 160]. The leading cause of mortality in women with endometrial cancer is cardiovascular disease [161]. Therefore, it is hypothesized that obese women with endometrial cancer may have a higher mortality rate because of metabolic complications (e.g., insulin resistance and chronic inflammation) [89]. Indeed, a meta-analysis of all-cause mortality in cancer patients reported a hazard ratio of 1.76 (95 % CI 1.34–2.31) for diabetic versus non-diabetic women with endometrial cancer [162]. Bjorge et al. [28] reported an increased risk of mortality due to endometrial cancer in individuals with metabolic syndrome, greater BMI, hypertension and triglyceride levels. Despite evidence suggesting increased endometrial cancer risk as a result of obesity-related metabolic complications, the mechanism by which these complications may affect endometrial cancer recurrence and mortality requires further investigation [100].

6 Conclusion and Future Research Directions

There is abundant epidemiologic evidence demonstrating a strong and consistent association between obesity, as measured by BMI, and endometrial cancer risk. However, there is considerably less evidence on the effect of obesity on mortality (all-case and endometrial cancer-specific) among both healthy and endometrial cancer patient populations. Associations were even stronger when severe obesity was considered as observed effect estimates increased with both endometrial cancer risk and mortality. Increased waist circumference and waist-to-hip ratio

were also strongly associated with increased endometrial cancer risk in pooled analyses of studies from the literature. Additionally, studies tended to show that obesity during childhood/adolescence or early adulthood also increased risk of endometrial cancer. Weight gain in adult life and weight cycling were associated with an increased risk of endometrial cancer, while weight loss was a protective factor.

Since observational epidemiologic studies are prone to effects of confounding, reverse causation and measurement error, the true effect of obesity on cancer risk cannot always be assessed without bias. Mendelian randomization could provide a method by which the obesity to cancer association could be more accurately measured because of the strong genetic component of obesity [163, 164]. By controlling for genetic variants of obesity, it is possible to determine an unbiased estimate of the causal effect of obesity on cancer risk, if additional defined assumptions are maintained, including that the genetic variant only affects cancer through its effects on obesity. However, measurement of genetic variants requires genotyping and identification of gene loci associated with obesity; thus, there have been very few studies on Mendelian randomization with respect to obesity and cancer risk [165, 166, 167]. These studies have provided mixed results, and there are very limited studies with respect to endometrial cancer. One study by Nead et al. [122] has since demonstrated a causal effect of increased insulin levels with endometrial cancer risk using Mendelian randomization. Further studies using Mendelian randomization can more accurately determine the true casual effect of obesity on endometrial cancer risk.

As the epidemic of childhood obesity continues globally [168, 169], it is of increasing importance to understand the effects of early-life obesity on future disease risk. In this literature review, there were very few studies on the effect of childhood obesity on endometrial cancer risk and no studies on endometrial cancer mortality. The few studies to date suggest an increased risk of endometrial cancer with early-life obesity [43, 54, 79]; however, these studies were limited by self-reported approximations of childhood obesity. Additional studies on the effect of childhood obesity on endometrial cancer risk and survival using more accurate measures of obesity are necessary to better quantify this relation. Furthermore, the effects of weight gain or loss and weight cycling can aid in providing mechanistic insight into the risk of cancer associated with obesity [170].

There has been some evidence demonstrating the differential effect of obesity on Type I versus Type II endometrial cancers, since obesity is a stronger risk factor for Type I endometrial cancers and does indeed show a stronger association with Type I endometrial cancers in most studies [24, 66, 70, 85, 171, 172]. When considering other histological tumor subtypes, stronger associations of obesity–endometrial cancer risk have been found in endometrioid adenocarcinomas compared to other carcinomas or uterine sarcomas [55, 59, 66, 73, 173]. Several endometrial tumor molecular phenotypes have also been examined for potential effect modification in the obesity–endometrial cancer association. Amankwah et al. [171] demonstrated a stronger association between obesity and microsatellite-instable (MSI) tumors compared to microsatellite-stable (MSS) tumors. MSI endometrial cancers are indicative of impairment in DNA mismatch repair (MMR), and one study by Win et al. [174] has examined the effect of MMR gene mutations on early adulthood obesity and risk of endometrial cancer and found that there is an increased association in non-carriers compared to carriers. Evidence on histological or

molecular subtypes of endometrial tumors remains limited, and further studies will contribute to the understanding of the obesity–endometrial cancer association.

Some studies have examined differential effects of obesity on endometrial cancer risk within population subgroups [29, 34, 40, 43, 52, 55, 67, 68, 70, 72, 74, 75, 79, 80, 87, 175, 176]. There have been mixed findings in terms of menopausal status with some studies demonstrating a stronger obesity–endometrial cancer association in postmenopausal women [29, 68], in premenopausal women [34, 43] or no difference between groups [40, 55, 79]. Two studies have also examined the association, stratified by race and largely found no difference between groups [75, 175]. There appears to be a consensus among studies that the obesity–endometrial cancer association is stronger in never users of hormone therapy [67, 68, 70, 74, 79, 80] and oral contraceptives [40, 68, 87]. Lastly, there have also been inconsistent findings on potential effect modification by increased physical activity, with some studies showing a stronger obesity–endometrial cancer association in inactive women [52, 176] and other studies observing no difference based on physical activity levels [55, 72, 87]. A limited number of studies have examined modifying effects of other risk factors, and further research is needed to provide additional mechanistic insights into the obesity–endometrial cancer association. Furthermore, certain population subgroups may have stronger obesity–endometrial cancer risk associations and would consequently have an increased benefit with a reduction in body weight.

Although a number of hypothesized biologic pathways linking obesity and endometrial cancer development have been previously discussed [89, 177], experimental studies are needed to establish the causal associations between these biologic risk factors and endometrial cancer development. Furthermore, assessments of biologic risk factors independently of obesity are needed, since many of the proposed risk factors may be present, or their effects amplified, as a result of excess adiposity. Well-powered intervention studies aimed at reducing excess adiposity may provide strong evidence on the biologic markers that indirectly affect endometrial cancer risk through excess adiposity. Finally, further studies are necessary to investigate the effects of biologic risk factors on endometrial cancer progression and survival. These additional studies will improve our understanding of the proposed biologic pathways and aid in developing more efficient strategies for endometrial cancer prevention.

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