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Understanding Obesity and Endometrial Cancer Risk: Opportunities for Prevention

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Abstract

Worldwide, obesity has become a major public health crisis. Overweight and obesity not only increase the risk of cardiovascular disease and type-2 diabetes, but also are now known risk factors for a variety of cancer types. Among all cancers, increasing body mass index is most strongly associated with endometrial cancer incidence and mortality. The molecular mechanisms underlying how adipose tissue and obesity contribute to the pathogenesis of endometrial cancer are becoming better understood and have revealed a number of rational strategies, both behavioral and pharmaceutical, for the prevention of both primary and recurrent disease.

Keywords

endometrial cancer; estrogen; insulin; obesity; prevention

Obesity and Endometrial Cancer Risk: Mechanisms and Rational Strategies for Cancer Prevention

Obesity is a well-established risk factor for the development of multiple types of cancer, cancer-related mortality, and all-cause mortality^{1, 2}. Among all cancers, increasing body mass index (BMI) and obesity is most strongly associated with endometrial cancer incidence and mortality¹. In a recent meta-analysis of 19 reviews and prospective studies, Renehan *et al.* found that each increase in BMI of 5 kg/m² significantly increased a woman's risk of developing endometrial cancer (RR 1.59, 95% CI 1.50-1.68)³. In the Million Women Study conducted in the U.K the investigators found that increasing BMI was associated with increased incidence of endometrial cancer (trend in relative risk per 10-units = 2.89, 95% CI 2.62-3.18)¹. Endometrial cancer mortality is also adversely impacted by obesity. Calle *et al.*,

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in a prospective study of over 495,000 women followed for 16 years, showed a significantly increased risk of death in obese women with endometrial cancer. Even more striking was the trend associated with increasing BMI; the relative risk of uterine cancer-related death for women considered obese (BMI 30-34.9 kg/m²) was 2.53 while for morbidly obese women (BMI > 40 kg/m²) it was 6.25⁴. Not only does obesity impact cancer-related death, but through its association with other medical co-morbidities, such as diabetes mellitus and hypertension, it adversely impacts all-cause mortality. In a retrospective review of 380 patients with early endometrial cancer, the Gynecologic Oncology Group (GOG) found that morbid obesity was associated with a higher mortality (HR 2.77, 95% CI 1.21-6.36) from causes other than endometrial cancer or disease recurrence⁵. Further complicating matters, there is limited public knowledge of the relationship between obesity and cancer risk. A recent survey indicated that up to 58% of women were not aware that obesity increased endometrial cancer risk⁶.

While it has been presumed that excess estrogen due to the peripheral conversion of androstenedione to estrone accounts for the increased risk of endometrial cancer in obese women, new studies implicate other mechanisms by which obesity promotes endometrial cancer. This review will discuss the current understanding of what factors underlie the association of obesity and endometrial cancer, and what strategies are available for both prevention and treatment.

Obesity and Hormone Imbalance

Estrogen is a known endometrial growth factor. While the ovaries are the primary source of estrogen in pre-menopausal women, peripheral tissues including adipose tissue become the primary sources of circulating estrogen in post-menopausal women⁷⁻⁹. Androgens are converted to estrone and estradiol by the enzyme aromatase in adipose tissue. Aromatase is produced by mesenchymal stromal cells, including adipocyte stem cells, and to a lesser degree by mature adipocytes themselves. Aromatase levels increase as a function of age and obesity and are reflected by an increase in circulating estrogen levels with increasing BMI in postmenopausal women^{10, 11}. Cauley *et al*, demonstrated greater than 40% increases in both circulating estrone and estradiol in obese (BMI >30) versus normal (BMI < 27) post-menopausal women¹⁰. Furthermore, concentrations of estrogens in adipose tissue have been measured at levels several fold above that observed in plasma^{12, 13}. Therefore visceral adipose tissue represents not only a source of estrogen, but also provides an ideal milieu for the growth of metastatic, estrogen sensitive endometrial cancer. Furthermore, serum hormone binding globulin (SHBG) levels decrease with increasing adiposity¹⁴. This glycoprotein binds both estrogen and testosterone, and inhibits their activity. Therefore, irrespective of *de novo* synthesis, obesity can influence biologically active levels of these hormones.

Estrogen promotes the growth of endometrial cancer cells by both direct and indirect regulation of gene transcription. The binding to cytoplasmic estrogen receptors alpha and beta (ER α and ER β) leads to recruitment of transcriptional co-factors and the direct activation of a wide variety of estrogen responsive genes. Estrogen receptors can also bind in an estrogen-dependent and independent manner to other transcription factors and enhance

gene transcription through alternative response elements^{15, 16}. It is also apparent that estrogen itself exerts rapid, non-genomic effects, associated with a variety of cytoplasmic kinase signaling cascades^{16, 17}. 17 β -estradiol (E2) treatment activates both the PI3-kinase and MAPK pathways, which are associated with cellular proliferation, and are frequently hyperactivated in cancers. The direct association between estrogen receptors and cell surface receptors, including IGF-1R and EGFR, represents a mechanism that directly links estrogen to the downstream kinase cascades that promote cell growth and tumor progression.

In normal premenstrual endometrium, progesterone counters estrogen-driven proliferation and induces glandular differentiation and decidualization of the endometrial stroma. Conditions that are accompanied by prolonged progesterone deficiencies therefore promote endometrial proliferation and increase the risk of endometrial hyperplasia and its progression to endometrial cancer^{18,19}. For example, nulliparity, irregular menses, and extended, post-menopausal hormone replacement therapy with unopposed estrogen, are associated with increased endometrial cancer risk¹⁸⁻²⁰. In pre-menopausal obese women, lack of progesterone due to anovulation, such as that observed in polycystic ovarian syndrome (PCOS), is also likely to contribute to endometrial cancer risk.

PCOS is a heterogeneous disorder affecting 6-8% of women characterized by androgen excess, menstrual abnormalities due to ovulatory dysfunction, and is often associated with polycystic ovarian morphology²¹. Obesity is found in approximately 30 to 70% of women with PCOS²². A principle element of this disorder is the presence of insulin resistance, which is worsened by obesity. A recent Australian case-control study of women under the age of 50 years, has shown that women with PCOS had a four-fold greater risk of endometrial cancer as compared to women without PCOS²³. When adjusted for BMI, PCOS remained an independent risk factor and was associated with a greater than two-fold increased risk for endometrial cancer.

Type 2 Diabetes and Hyperinsulinemia

Hyperinsulinemia and the insulin resistant state are closely associated with obesity. Epidemiologically, a number of studies have shown a modest association of diabetes with endometrial cancer risk.²⁴⁻²⁸ Interestingly, in three studies the most significant risks were seen in women who were both obese and diabetic^{24, 27, 29}. A study by Troisi *et al* examined insulin levels in women with endometrial cancer compared to controls in order to determine if elevated insulin levels could explain the association of obesity and endometrial cancer³⁰. While elevated serum insulin levels, as measured by C-peptide were associated with increased risk of endometrial cancer, elevation of serum insulin levels *alone* could not account for the association of obesity and endometrial cancer.

Several recent studies, including one by our group, demonstrate an association of insulin resistance with endometrial cancer risk using adiponectin as surrogate marker for insulin resistance³¹⁻³⁴. This adipokine can be measured in serum or plasma, and demonstrates levels that are inversely proportional to insulin resistance. Using a case-control study design, our group found that low adiponectin levels were highly associated with endometrial cancer risk, independent of BMI. Subsequently, a large prospective, nested case-control study sponsored

by the World Health Organization, performed a study on adiponectin and endometrial cancer risk³⁴. All samples were collected prospectively, and those used for analysis were from a time point prior to the onset of endometrial cancer. This study confirmed that low adiponectin levels were associated with endometrial cancer risk, again independent of BMI, strongly suggesting that insulin resistance is an independent risk factor for endometrial cancer.

The specific effects of hyperinsulinemia on the pathogenesis of obesity-associated cancers are not well defined. Our group has demonstrated that the proliferative effect of estrogen on the endometrium is enhanced in obese versus lean animals³⁵. Using the Zucker rat model of hyperinsulinemia, estrogen induced significantly higher expression of the proproliferative genes, cyclin A and c-myc and in endometrium of obese rats, as compared that observed in lean control animals. Conversely, the estrogen-induced suppression of the cell cycle inhibitor, p27Kip1, and the anti-proliferative genes sFRP4 and RALDH2 are more pronounced in the obese endometrium. Obesity, therefore, alters the balance between pro- and anti-proliferative signals to favor endometrial growth.

Insulin-like Growth Factors

Systemic levels of IGFs are also altered by obesity. Six IGFBPs bind to and modulate IGF bioactivity by interfering with receptor binding. While increased estrogen production directly increases IGF-1 synthesis^{36,37} sustained hyperinsulinemia results in the decreased synthesis of IGFBP1 and 2⁷. IGFBP1 is most highly expressed by human endometrium^{38, 39}. Therefore, obesity contributes to the simultaneous increase in circulating IGF and decrease in IGFBP1, resulting in the *net increase* of bioavailable IGF-1^{7, 40, 41}.

Insulin and IGF Signaling Pathways

Insulin and IGFs utilize common signaling mechanisms⁴². As illustrated in figure 3, upon ligand binding, receptor mediated phosphorylation of the Insulin Receptor Substrate 1 (IRS-1) scaffold protein results in the activation of both the PI3K/AKT/mTOR and MAPK signaling pathways, which promote cell survival and proliferation⁴².

Hyperactivity of the PI3K/AKT/mTOR pathway is frequently observed in endometrial cancer. The ubiquitously expressed phosphatase and tensin homolog (PTEN) lipid/protein phosphatase dephosphorylates PI3K substrates and acts as a PI3K antagonist and tumor suppressor gene. PTEN inactivation or loss is observed in greater than 40% of type I endometrial cancers. Therefore, coupled with elevated circulating IGF-1, the loss of PTEN promotes the hyperactivity of the PI3K/AKT/mTOR pathway and facilitates endometrial cancer growth in obese individuals. Furthermore, the insulin and IGF receptors simultaneously activate the MAPK signaling pathway, another mechanism that promotes mTOR signaling⁴².

AMPK (5' adenosine monophosphate-activated protein kinase) inhibits signaling through the PI3K/AKT/mTOR pathway by serving as a counterbalance to AKT and ERK activity. AMPK *inactivation* is commonly associated with obesity (energy/caloric excess) and insulin resistance. When phosphorylated by AMPK, the tuberous sclerosis complex (TSC1/2)

prevents mTOR-mediated endometrial proliferation. Inactivation of AMPK therefore represents an additional mechanism contributing to the hyperactivity of mTOR and tumorigenesis in the endometrium.

Adipokines

Adipose tissue is a complex endocrine organ that secretes a variety of both anti- and pro-inflammatory factors classified as “adipokines”. The state of chronic systemic inflammation associated with obesity is increasingly linked to the development of insulin resistance and chronic hyperinsulinemia⁴³⁻⁴³. For example, secretion of the adipokine, TNF α disrupts insulin receptor signaling by inducing the inhibitory phosphorylation of IRS proteins, thereby uncoupling insulin from downstream signaling cascades⁴⁴, is associated with In addition to TNF α ⁴⁵, additional pro-inflammatory adipokines associated with endometrial cancer include include leptin⁴⁶, interleukin-6 (IL-6)⁴⁷ and resistin⁴⁸.

In opposition to the pro-inflammatory adipokines, circulating levels of adiponectin are inversely proportional to BMI and insulin resistance, and play a role in increasing insulin sensitivity and as an anti-inflammatory. Adiponectin signals through its receptors (AdipoR1/2) to activate AMPK and inhibit PI3K/AKT/mTOR signaling⁴⁹, and should therefore inhibit tumor progression driven by the PI3K pathway. In support of this hypothesis, studies performed by our group and others confirm that adiponectin levels are independently and inversely associated with endometrial cancer risk³¹⁻³⁴.

Adipokines and other inflammatory proteins associated with obesity, such as C-reactive protein, show promise as biomarkers of endometrial cancer risk⁵⁰⁻⁵², however, additional studies will be necessary to determine the complex roles of adipokines in the development of insulin resistance and obesity-associated endometrial cancer.

Rational Interventions

These known biochemical mechanisms by which overweight and obesity contribute to endometrial cancer risk suggest several rational strategies for cancer prevention. These include behavioral, pharmaceutical and surgical interventions that prevent or reverse the hormonal and metabolic imbalances associated with obesity and insulin resistance.

Oral Contraceptives

Multiple epidemiologic studies demonstrate that women who use combination estrogen and progesterone oral contraceptives (OCP) decrease their risk of endometrial cancer by 50%^{53, 54, 55}. While there is no data to support a decreased efficacy in endometrial cancer protection in obese women, there are studies that suggest that obese women have a slightly decreased contraceptive efficacy compared to thin women⁵⁶. A study by Maxwell *et al* found that OCP with higher potency progestins may be more effective for women with a higher BMI⁵⁷. More data will be necessary to refine the optimal OCP for endometrial cancer chemoprevention in an obese population.

The levonorgestrel containing IUD (LNG-IUD) is also an attractive candidate for endometrial cancer prevention. The use of IUDs alone is associated with a lower risk of endometrial cancer⁵⁸, and the progestin may further protect the endometrium. A few studies have reported the use of the LNG-IUD for reversal of endometrial hyperplasia and cancer, but additional data will be necessary before it can be recommended for cancer prevention.

Synthetic progestogens are commonly used in oral contraceptives and intrauterine devices, and for the treatment of menorrhagia, infertility, and the symptoms of menopause. Progestin therapy is also standard for the treatment of women who have endometrial hyperplasia without atypia, a likely precursor lesion for endometrial cancer⁵⁹. The response of complex hyperplasia with atypia and well-differentiated endometrial carcinoma to progestin has also been investigated. In studies performed by Wheeler *et al*, complete remission was observed in 67% of women with complex atypical hyperplasia, while 11% regressed to complex hyperplasia without atypia, and 22% had persistent disease with a median follow-up of 11-months⁵⁹. In women with well-differentiated endometrial carcinoma, 42% of women demonstrated a complete remission, while 58% had persistent disease over a 12-month follow up period.

Behavioral: Diet and Exercise

Body mass and physical activity are modifiable risk factors, which can be manipulated to favorably impact cancer patient outcome. A recent study of 42,672 post-menopausal women enrolled in the American Cancer Society Cancer Prevention Study II Nutrition Cohort, evaluated the incidence of endometrial cancer in relation to physical activity and BMI⁶⁰. During the period between 1992 and 2003, a total of 466 new cases of endometrial cancer were diagnosed. Recreational and moderate physical activity was associated with a 33% lower endometrial cancer risk, and the effect was pronounced among women who were overweight or obese.

Circulating estrogen levels correlate with increasing BMI in post-menopausal women, while weight loss either by dietary changes or exercise or a combination thereof reduce estrogen synthesis. Both caloric restriction, as well as the source of calories appears to influence serum hormone concentration. High-fiber, low-fat diet interventions have been shown to lower bioavailable concentration of estradiol in breast cancer survivors even in the absence of concurrent weight loss^{61,62, 63}.

Physical activity consistently demonstrates a pronounced effect on hormone levels in both lean and obese individuals⁶⁴⁻⁶⁵ and is associated with a decreased risk of post-menopausal breast cancer, as well as breast cancer recurrence. However, diet and exercise are also known to prevent recurrence of tumors types typically unresponsive to hormones, including estrogen-receptor negative breast cancer, suggesting that additional pathways activated by physical activity and diet influence tumor growth^{66, 67}.

Weight loss, whether by behavioral changes (diet and exercise) or by surgery, is known to reverse insulin resistance, decrease bioactive IGF-1 levels and prevent the onset of type 2 diabetes. Recently, Pendyala *et al* conducted expression profiling on rectosigmoid mucosal biopsies obtained from obese women pre and post diet-induced weight loss⁶⁸. Following a

10% weight loss, tissues demonstrated significant decreases in a variety of inflammatory cytokines including TNF α , IL-6, IL-8, and MCP-1, as well downregulation of markers of proinflammatory pathways, prostaglandin metabolism and transcription factors. This was reflected by decreases in circulating TNF α and IL-8 as well as serum glucose, cholesterol and triglycerides, and lower T-cell and macrophage counts in tissues. Taken together, this data suggest that weight loss reduces colorectal inflammation and uncouples cancer promoting signaling pathways, thereby reducing colorectal cancer risk. In addition to their effects on insulin, IGF and inflammatory signaling, caloric restriction and exercise activate AMPK as a consequence of a systemic increase in AMP secondary to ATP depletion. It is probable that weight loss can play a therapeutic role in the prevention of all obesity-associated cancer types.

Metabolic/Bariatric Surgery

Modest weight loss of 5-10% of body weight through diet and exercise reduces the incidence of type 2 diabetes and other co-morbidities associated with obesity, and is currently recommended as a weight loss goal by the American Cancer Society for overweight cancer survivors⁶⁹. Unfortunately, the significant lifestyle changes associated with weight loss are difficult to adopt and maintain for many obese and morbidly obese individuals, and many are unsuccessful in maintaining a healthy weight.

By producing a sustained weight loss, bariatric surgery has recently been demonstrated to reduce both cancer risk and recurrence⁷⁰. Sjostrom *et al* have demonstrated a reduced cancer risk in a 10-year follow up of individuals in Sweden who underwent bariatric surgery⁷¹. Interestingly, this effect favored women (RR 0.58, 95% CI 0.44-0.77) over men (RR 0.97, 0.62-1.52). A larger study performed by Adams *et al*, demonstrated a decreased incidence of cancer in 6,596 U.S. subjects who underwent gastric bypass surgery (HR 0.76, 95% CI 0.65-0.89, $p = 0.006$)⁷². In agreement with the Swedish study, bariatric surgery produced a more pronounced cancer-preventive effect in women (HR 0.73, 95% CI 0.62-0.87, $p = 0.0004$) over men (HR 1.02, 0.69-1.52, $p = 0.91$). The hazard ratio of endometrial cancer was dramatically reduced to 0.22 (95% CI 0.13-0.40, $p < 0.0001$). These data underscore the profound effect of obesity on endometrial cancer risk and suggest that weight loss, whether by behavioral change or surgical intervention, is critical to endometrial cancer prevention.

Antidiabetic Agents: Metformin

Metformin is an oral anti-hyperglycemic drug long used in the management of type-2 diabetes⁷³. Metformin lowers blood glucose levels by inhibiting gluconeogenesis and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Based on its positive effect on increasing insulin sensitivity, metformin represents a rational chemopreventive agent for endometrial and other obesity-associated cancers. Additional studies suggest the chemopreventive and therapeutic benefits of metformin are mediated through activation of the growth inhibitory AMPK pathway⁷⁴⁻⁷⁵, thereby counteracting the PI3K/AKT/mTOR signaling, as illustrated in figure 3.

These mechanisms of action suggest a promising and novel role for this “old drug” in the chemoprevention of primary and recurrent tumors^{76, 77}. Indeed, this has been demonstrated by retrospective epidemiologic studies. Li *et al* have demonstrated that diabetic patients who had taken metformin had a significantly lower risk of pancreatic cancer compared with those who had not⁷⁸. Furthermore, diabetic breast cancer patients receiving metformin demonstrate a greater incidence of pathologic complete response to neoadjuvant therapy⁷⁹. Metformin use is also associated with a decrease in prostate cancer risk⁸⁰.

Recently, metformin has further been shown to inhibit aromatase expression by primary cultures of human adipose stromal cells⁸¹. If this effect hold true *in vivo*, we expect that metformin would inhibit the localized production of estrogens in tumor stromal tissue and also decrease circulating levels of estrogen observed in obese individuals. Metformin has also been shown to increase progesterone receptor expression in endometrial cancer cell lines⁸² and in breast cancer patients⁸³. It is possible, therefore, that metformin augments the anti-proliferative effects of progestins by virtue of amplified PR signaling.

While the multiple mechanisms of action of metformin have biological plausibility for its use as a chemopreventive agent for cancer in general, it is an ideal drug choice for the primary and tertiary prevention of endometrial cancer.

Summary

Current evidence suggests that by targeting the hormonal imbalances and hyperactive proliferative pathways associated with obesity, the lifetime risk of endometrial cancer can be significantly reduced. While achieving and maintaining a healthy body weight by diet and exercise represents the ideal solution to endometrial cancer prevention, the reality of the worldwide obesity epidemic necessitates the availability of pharmaceutical and surgical alternatives to reduce the impact of obesity on endometrial cancer risk.

REFERENCES

1. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ*. 2007; 335:1134. [PubMed: 17986716]
2. Bessonova L, Marshall SF, Ziogas A, et al. The association of body mass index with mortality in the california Teachers Study. *Int J Cancer*.
3. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008; 371:569–78. [PubMed: 18280327]
4. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003; 348:1625–38. [PubMed: 12711737]
5. Von Gruenigen VE, Tian C, Frasure H, Waggoner S, Keys H, Barakat RR. Treatment effects, disease recurrence, and survival in obese women with early endometrial carcinoma : a Gynecologic Oncology Group study. *Cancer*. 2006; 107:2786–91. [PubMed: 17096437]
6. Soliman PT, Bassett RL Jr. Wilson EB, et al. Limited public knowledge of obesity and endometrial cancer risk: what women know. *Obstet Gynecol*. 2008; 112:835–42. [PubMed: 18827126]
7. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer*. 2004; 4:579–91. [PubMed: 15286738]

8. Boon WC, Chow JD, Simpson ER. The multiple roles of estrogens and the enzyme aromatase. *Prog Brain Res.* 2010; 181:209–32. [PubMed: 20478440]
9. Van Kruijsdijk RC, Van Der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. *Cancer Epidemiol Biomarkers Prev.* 2009; 18:2569–78. [PubMed: 19755644]
10. Cauley JA, Gutai JP, Kuller LH, Ledonne D, Powell JG. The epidemiology of serum sex hormones in postmenopausal women. *Am J Epidemiol.* 1989; 129:1120–31. [PubMed: 2729251]
11. Simpson ER, Mendelson CR. Effect of aging and obesity on aromatase activity of human adipose cells. *Am J Clin Nutr.* 1987; 45:290–5. [PubMed: 3799519]
12. Szymczak J, Milewicz A, Thijssen JH, Blankenstein MA, Daroszewski J. Concentration of sex steroids in adipose tissue after menopause. *Steroids.* 1998; 63:319–21. [PubMed: 9618794]
13. Geisler J. Breast cancer tissue estrogens and their manipulation with aromatase inhibitors and inactivators. *J Steroid Biochem Mol Biol.* 2003; 86:245–53. [PubMed: 14623518]
14. Morisset AS, Blouin K, Tchernof A. Impact of diet and adiposity on circulating levels of sex hormone-binding globulin and androgens. *Nutr Rev.* 2008; 66:506–16. [PubMed: 18752474]
15. O'lane R, Frith MC, Karlsson EK, Hansen U. Genomic targets of nuclear estrogen receptors. *Mol Endocrinol.* 2004; 18:1859–75. [PubMed: 15031323]
16. Marino M, Galluzzo P, Ascenzi P. Estrogen signaling multiple pathways to impact gene transcription. *Curr Genomics.* 2006; 7:497–508. [PubMed: 18369406]
17. Marino M, Ascenzi P, Acconcia F. S-palmitoylation modulates estrogen receptor alpha localization and functions. *Steroids.* 2006; 71:298–303. [PubMed: 16274718]
18. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev.* 2002; 11:1531–43. [PubMed: 12496040]
19. Schindler AE. Progestogen deficiency and endometrial cancer risk. *Maturitas.* 2009; 62:334–7. [PubMed: 19231117]
20. Papaioannou S, Tzafettas J. Anovulation with or without PCO, hyperandrogenaemia and hyperinsulinaemia as promoters of endometrial and breast cancer. *Best Pract Res Clin Obstet Gynaecol.* 2010; 24:19–27. [PubMed: 19264556]
21. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. *Nat Rev Endocrinol.* 2011
22. Vrbikova J, Hainer V. Obesity and polycystic ovary syndrome. *Obes Facts.* 2009; 2:26–35. [PubMed: 20054201]
23. Fearnley EJ, Marquart L, Spurdle AB, Weinstein P, Webb PM. Polycystic ovary syndrome increases the risk of endometrial cancer in women aged less than 50 years: an Australian case-control study. *Cancer Causes Control.* 2010; 21:2303–8. [PubMed: 20953904]
24. Shoff SM, Newcomb PA. Diabetes, body size, and risk of endometrial cancer. *Am J Epidemiol.* 1998; 148:234–40. [PubMed: 9690359]
25. Weiderpass E, Persson I, Adami HO, Magnusson C, Lindgren A, Baron JA. Body size in different periods of life, diabetes mellitus, hypertension, and risk of postmenopausal endometrial cancer (Sweden). *Cancer Causes Control.* 2000; 11:185–92. [PubMed: 10710204]
26. Anderson KE, Anderson E, Mink PJ, et al. Diabetes and endometrial cancer in the Iowa women's health study. *Cancer Epidemiol Biomarkers Prev.* 2001; 10:611–6. [PubMed: 11401910]
27. Salazar-Martinez E, Lazcano-Ponce EC, Lira-Lira GG, et al. Case-control study of diabetes, obesity, physical activity and risk of endometrial cancer among Mexican women. *Cancer Causes Control.* 2000; 11:707–11. [PubMed: 11065007]
28. Parazzini F, La Vecchia C, Negri E, et al. Diabetes and endometrial cancer: an Italian case-control study. *Int J Cancer.* 1999; 81:539–42. [PubMed: 10225441]
29. Friberg E, Mantzoros CS, Wolk A. Diabetes and risk of endometrial cancer: a population-based prospective cohort study. *Cancer Epidemiol Biomarkers Prev.* 2007; 16:276–80. [PubMed: 17301260]
30. Troisi R, Potischman N, Hoover RN, Siiteri P, Brinton LA. Insulin and endometrial cancer. *Am J Epidemiol.* 1997; 146:476–82. [PubMed: 9290508]
31. Soliman PT, Wu D, Tortolero-Luna G, et al. Association between adiponectin, insulin resistance, and endometrial cancer. *Cancer.* 2006; 106:2376–81. [PubMed: 16639730]

32. Dal Maso L, Augustin LS, Karalis A, et al. Circulating adiponectin and endometrial cancer risk. *J Clin Endocrinol Metab.* 2004; 89:1160–3. [PubMed: 15001602]
33. Petridou E, Mantzoros C, Dessypris N, et al. Plasma adiponectin concentrations in relation to endometrial cancer: a case-control study in Greece. *J Clin Endocrinol Metab.* 2003; 88:993–7. [PubMed: 12629074]
34. Cust AE, Kaaks R, Friedenreich C, et al. Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. *J Clin Endocrinol Metab.* 2007; 92:255–63. [PubMed: 17062769]
35. Zhang Q, Shen Q, Celestino J, et al. Enhanced estrogen-induced proliferation in obese rat endometrium. *Am J Obstet Gynecol.* 2009; 200:186, e1–8. [PubMed: 19185100]
36. Klotz DM, Hewitt SC, Ciana P, et al. Requirement of estrogen receptor- α in insulin-like growth factor-1 (IGF-1)-induced uterine responses and in vivo evidence for IGF-1/estrogen receptor cross-talk. *J Biol Chem.* 2002; 277:8531–7. [PubMed: 11751931]
37. Hewitt SC, Li Y, Li L, Korach KS. Estrogen-mediated regulation of Igf1 transcription and uterine growth involves direct binding of estrogen receptor α to estrogen-responsive elements. *J Biol Chem.* 2010; 285:2676–85. [PubMed: 19920132]
38. Rutanen EM. Insulin-like growth factors in endometrial function. *Gynecol Endocrinol.* 1998; 12:399–406. [PubMed: 10065165]
39. Rutanen EM. Insulin-like growth factors and insulin-like growth factor binding proteins in the endometrium. Effect of intrauterine levonorgestrel delivery. *Hum Reprod.* 2000; 15(Suppl 3):173–81. [PubMed: 11041233]
40. Cust AE, Allen NE, Rinaldi S, et al. Serum levels of C-peptide, IGFBP-1 and IGFBP-2 and endometrial cancer risk; results from the European prospective investigation into cancer and nutrition. *Int J Cancer.* 2007; 120:2656–64. [PubMed: 17285578]
41. Lukanova A, Zeleniuch-Jacquotte A, Lundin E, et al. Prediagnostic levels of C-peptide, IGF-I, IGFBP -1, -2 and -3 and risk of endometrial cancer. *Int J Cancer.* 2004; 108:262–8. [PubMed: 14639613]
42. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer.* 2008; 8:915–28. [PubMed: 19029956]
43. Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. *Gastroenterology.* 2007; 132:2169–80. [PubMed: 17498510]
44. Nieto-Vazquez I, Fernandez-Veledo S, Kramer DK, Vila-Bedmar R, Garcia-Guerra L, Lorenzo M. Insulin resistance associated to obesity: the link TNF- α . *Arch Physiol Biochem.* 2008; 114:183–94. [PubMed: 18629684]
45. Shaarawy M, Abdel-Aziz O. Serum tumour necrosis factor α levels in benign and malignant lesions of the endometrium in postmenopausal women. A preliminary study. *Acta Oncol.* 1992; 31:417–20. [PubMed: 1632976]
46. Cymbaluk A, Chudecka-Glaz A, Rzepka-Gorska I. Leptin levels in serum depending on Body Mass Index in patients with endometrial hyperplasia and cancer. *Eur J Obstet Gynecol Reprod Biol.* 2008; 136:74–7. [PubMed: 17007993]
47. Ferdeghini M, Gadducci A, Prontera C, et al. Serum interleukin-6 levels in uterine malignancies. Preliminary data. *Anticancer Res.* 1994; 14:735–7. [PubMed: 8010733]
48. Hlavna M, Kohut L, Lipkova J, et al. Relationship of resistin levels with endometrial cancer risk. *Neoplasma.* 2011; 58:124–8. [PubMed: 21275461]
49. Long YC, Zierath JR. AMP-activated protein kinase signaling in metabolic regulation. *J Clin Invest.* 2006; 116:1776–83. [PubMed: 16823475]
50. Dossus L, Rinaldi S, Becker S, et al. Obesity, inflammatory markers, and endometrial cancer risk: a prospective case-control study. *Endocr Relat Cancer.* 17:1007–19. [PubMed: 20843938]
51. Wang T, Rohan TE, Gunter MJ, et al. A Prospective Study of Inflammation Markers and Endometrial Cancer Risk in Postmenopausal Hormone Non-Users. *Cancer Epidemiol Biomarkers Prev.*
52. Wen W, Cai Q, Xiang YB, et al. The modifying effect of C-reactive protein gene polymorphisms on the association between central obesity and endometrial cancer risk. *Cancer.* 2008; 112:2409–16. [PubMed: 18383516]

53. Kaufman DW, Shapiro S, Slone D, et al. Decreased risk of endometrial cancer among oral-contraceptive users. *N Engl J Med*. 1980; 303:1045–7. [PubMed: 7421893]
54. Beral V, Hannaford P, Kay C. Oral contraceptive use and malignancies of the genital tract. Results from the Royal College of General Practitioners' Oral Contraception Study. *Lancet*. 1988; 2:1331–5. [PubMed: 2904052]
55. Combination oral contraceptive use and the risk of endometrial cancer. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. *JAMA*. 1987; 257:796–800. [PubMed: 3027423]
56. Lopez LM, Grimes DA, Chen-Mok M, Westhoff C, Edelman A, Helmerhorst FM. Hormonal contraceptives for contraception in overweight or obese women. *Cochrane Database Syst Rev*. 2010; 7:CD008452. [PubMed: 20614470]
57. MAXWELL GL, SCHILDKRAUT JM, CALINGAERT B, et al. Progestin and estrogen potency of combination oral contraceptives and endometrial cancer risk. *Gynecol Oncol*. 2006; 103:535–40. [PubMed: 16740300]
58. Beining RM, Dennis LK, Smith EM, Dokras A. Meta-analysis of intrauterine device use and risk of endometrial cancer. *Ann Epidemiol*. 2008; 18:492–9. [PubMed: 18261926]
59. Wheeler DT, Bristow RE, Kurman RJ. Histologic alterations in endometrial hyperplasia and well-differentiated carcinoma treated with progestins. *Am J Surg Pathol*. 2007; 31:988–98. [PubMed: 17592264]
60. Patel AV, Feigelson HS, Talbot JT, et al. The role of body weight in the relationship between physical activity and endometrial cancer: results from a large cohort of US women. *Int J Cancer*. 2008; 123:1877–82. [PubMed: 18651569]
61. Rock CL, Flatt SW, Thomson CA, et al. Effects of a high-fiber, low-fat diet intervention on serum concentrations of reproductive steroid hormones in women with a history of breast cancer. *J Clin Oncol*. 2004; 22:2379–87. [PubMed: 15197199]
62. Key TJ, Allen NE, Spencer EA, Travis RC. Nutrition and breast cancer. *Breast*. 2003; 12:412–6. [PubMed: 14659114]
63. Key TJ, Appleby PN, Reeves GK, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst*. 2003; 95:1218–26. [PubMed: 12928347]
64. McTiernan A, Wu L, Chen C, et al. Relation of BMI and physical activity to sex hormones in postmenopausal women. *Obesity (Silver Spring)*. 2006; 14:1662–77. [PubMed: 17030978]
65. Friedenreich CM, Woolcott CG, McTiernan A, et al. Alberta physical activity and breast cancer prevention trial: sex hormone changes in a year-long exercise intervention among postmenopausal women. *J Clin Oncol*. 2010; 28:1458–66. [PubMed: 20159820]
66. McTiernan A. Mechanisms linking physical activity with cancer. *Nat Rev Cancer*. 2008; 8:205–11. [PubMed: 18235448]
67. McTiernan A, Irwin M, Vongruenigen V. Weight, physical activity, diet, and prognosis in breast and gynecologic cancers. *J Clin Oncol*. 2010; 28:4074–80. [PubMed: 20644095]
68. Pendyala S, Neff LM, Suarez-Farinas M, Holt PR. Diet-induced weight loss reduces colorectal inflammation: implications for colorectal carcinogenesis. *Am J Clin Nutr*. 2011; 93:234–42. [PubMed: 21147860]
69. Doyle C, Kushi LH, Byers T, et al. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin*. 2006; 56:323–53. [PubMed: 17135691]
70. Ashrafian H, Ahmed K, Rowland SP, et al. Metabolic surgery and cancer: protective effects of bariatric procedures. *Cancer*.
71. Sjostrom L, Gummesson A, Sjostrom CD, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *Lancet Oncol*. 2009; 10:653–62. [PubMed: 19556163]
72. Adams TD, Stroup AM, Gress RE, et al. Cancer incidence and mortality after gastric bypass surgery. *Obesity (Silver Spring)*. 2009; 17:796–802. [PubMed: 19148123]
73. Ungar G, Freedman L, Shapiro SL. Pharmacological studies of a new oral hypoglycemic drug. *Proc Soc Exp Biol Med*. 1957; 95:190–2. [PubMed: 13432032]

74. Zhou G, Myers R, LI Y, et al. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest*. 2001; 108:1167–74. [PubMed: 11602624]
75. Jalving M, Gietema JA, Lefrandt JD, et al. Metformin: taking away the candy for cancer? *Eur J Cancer*. 2010; 46:2369–80. [PubMed: 20656475]
76. Engelman JA, Cantley LC. Chemoprevention meets glucose control. *Cancer Prev Res (Phila)*. 2010; 3:1049–52. [PubMed: 20810671]
77. Ben Sahra I, Le Marchand-Brustel Y, Tanti JF, Bost F. Metformin in cancer therapy: a new perspective for an old antidiabetic drug? *Mol Cancer Ther*. 2010; 9:1092–9. [PubMed: 20442309]
78. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology*. 2009; 137:482–8. [PubMed: 19375425]
79. Jiralerspong S, Palla SL, Giordano SH, et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. *J Clin Oncol*. 2009; 27:3297–302. [PubMed: 19487376]
80. Wright JL, Stanford JL. Metformin use and prostate cancer in Caucasian men: results from a population-based case-control study. *Cancer Causes Control*. 2009; 20:1617–22. [PubMed: 19653109]
81. Brown KA, Hunger NI, Docanto M, Simpson ER. Metformin inhibits aromatase expression in human breast adipose stromal cells via stimulation of AMP-activated protein kinase. *Breast Cancer Res Treat*. 2010; 123:591–6. [PubMed: 20300828]
82. Xie Y, Wang YL, Yu L, et al. Metformin promotes progesterone receptor expression via inhibition of mammalian target of rapamycin (mTOR) in endometrial cancer cells. *J Steroid Biochem Mol Biol*.
83. Bernstein LM, Boyarkina MP, Tsyrlina EV, Turkevich EA, Semiglazov VF. More favorable progesterone receptor phenotype of breast cancer in diabetics treated with metformin. *Med Oncol*. 2010

Figure 1. Overview

The contribution of obesity to endometrial cancer progression and preventive strategies.

Figure 2. The systemic effects of obesity on endometrial cancer initiation and progression
Increased adiposity and inflammation coupled with the decrease in adiponectin synthesis, contribute to insulin resistance. This leads to hyperglycemia and a further compensatory increase in insulin synthesis. Hyperinsulinemia is associated with the decreased synthesis of IGF binding proteins, and increased IGF bioavailability. The simultaneous increase in estrogen production promotes additional IGF-1 synthesis. Signaling through the IGF-1R promotes endometrial proliferation with an increased risk of endometrial cancer.

Figure 3. Insulin and IGF-1 signaling drive endometrial cancer progression

The binding of IGF-1 to its receptor leads to IGF-1R autophosphorylation and the subsequent activation of multiple downstream signaling pathways. Cellular proliferation is driven through the PI3K and the MAPK pathways. Behavioral and pharmaceutical interventions, which decrease adiposity and IGF-1 levels, and that activate AMPK, and therefore represent rational therapeutic strategies for the prevention of endometrial cancer.