VOLUME 34 · NUMBER 35 · DECEMBER 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Addressing the Role of Obesity in Endometrial Cancer Risk, Prevention, and Treatment

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Published online ahead of print at www.jco.org on November 7, 2016.

Supported in part by Grant No. P50CA098258 from the National Cancer Institute and also in part by the National Institutes of Health through The University of Texas MD Anderson Cancer Center Support Grant No. CA016672.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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0732-183X/16/3435w-4225w/$20.00

DOI: 10.1200/JCO.2016.69.4638

ABSTRACT

In sharp contrast to many other cancer types, the incidence and mortality of endometrial cancer continue to grow. This unfortunate trend is, in no small part, a result of the worldwide obesity epidemic. More than half of endometrial cancers are currently attributable to obesity, which is recognized as an independent risk factor for this disease. In this review, we identify the molecular mechanisms by which obesity and adipose tissue contribute to the pathogenesis of endometrial cancer. We further discuss the impact of obesity on the clinical management of the disease and examine the development of rational behavioral and pharmaceutical interventions aimed at reducing endometrial cancer risk, improving cancer outcomes, and preserving fertility in an increasingly younger population of patients with endometrial cancer.

J Clin Oncol 34:4225-4230. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Among women, obesity is more strongly associated with the development of endometrial cancer than any other cancer type.[1] In fact, approximately 57% of endometrial cancers in the United States are thought to be attributable to being overweight and obese.[2,3] This association has been well established and follows a dose-response relationship, with the incidence of endometrial cancer increasing as body mass index (BMI) increases. In a meta-analysis of 26 studies by the American Institute for Cancer Research, for every increase of five BMI units, there was a 50% increase in the risk of developing endometrial cancer (relative risk [RR], 1.50; 95% CI, 1.42 to 1.59).[4] Endometrioid endometrial cancer is the histologic subtype predominantly linked to obesity; however, the incidence of more aggressive, nonendometrioid subtypes (such as serous, clear cell, and carcinosarcoma) has also recently been found to increase with increasing BMI.[5]

Once diagnosed with endometrial cancer, being obese portends worse outcomes. Compared with women with a normal BMI, the RR of disease-specific mortality for obese women with a BMI of 30 to 34.9 kg/m^2 is 2.53, and even more strikingly, for morbidly obese women with a BMI greater than 40 kg/m^2, the RR is 6.25.[6] Furthermore, obesity has a negative impact on all-cause mortality. In a retrospective study of women with early endometrial cancer, morbidly obese women had higher mortality rates compared with women with a normal BMI, and 67% of these deaths were a result of noncancerous, obesity-related causes.[7]

As rates of obesity among women continue to increase,[8] the incidence of endometrial cancer is expected to increase. A multivariate linear regression model, which accounts for expected changes in obesity, hysterectomy rates, and smoking tobacco, predicts that by the year 2030, the incidence of endometrial cancer will reach 42.13 cases per 100,000 women. This represents a staggering 55% increase over the incidence in 2010.[9]

Despite the clear evidence linking endometrial cancer and obesity, there is limited public awareness of this relationship. In a survey of 1,545 healthy women, 58% of participants were not aware that obesity increased the risk for developing endometrial cancer.[10] Women diagnosed with endometrial cancer or complex atypical hyperplasia (CAH), a precursor lesion to endometrial cancer, do not fare much better. One survey that included 43 women with endometrial cancer or CAH revealed that 46.5% of the women were unaware that obesity was a risk factor for their disease.[11] Furthermore, oncologists and other health care providers are often reluctant to counsel patients with endometrial cancer about obesity. In a separate survey of 108 women with endometrial cancer, only 29% reported being told by their health care

provider about the link between obesity and developing endometrial cancer. Interestingly, all of the women who were counseled about obesity by their oncologists attempted to lose weight.[12]

Although the association is not as strong as with endometrial cancer, it is interesting to note that the risk of developing other gynecologic malignancies may also be affected by obesity. Although the data have been mixed in prior studies, in a recent meta-analysis of 25 studies of more than 15,000 women, for every increase of five BMI units observed, there was a 6% increased risk in developing ovarian cancer.[13] A case-control study in France suggests that central adiposity (as measured by waist-to-hip circumference) may be a stronger risk factor for ovarian cancer than obesity as measured by BMI alone.[14] This relationship warrants additional study.

MECHANISTIC PATHWAYS LINKING OBESITY TO ENDOMETRIAL CANCER

Visceral fat is a complex endocrine organ, composed of adipocytes and preadipocytes, as well as infiltrating macrophages, stromal, nerve, and stem cells (Fig 1). Together, they secrete an array of adipokines that exert localized and systemic effects, which increase endometrial proliferation and promote tumorigenesis.[15-18] Furthermore, adipose tissue is a source of mesenchymal stem cells, which can be recruited to support tumor growth and progression.[19,20]

Unopposed Estrogen and the Relationship Between Obesity and Endometrial Cancer

In premenopausal women, the cyclic expression of estrogen by the ovaries drives endometrial proliferation.[21] After menopause, peripheral tissues, especially adipose tissue, become the main site of estrogen synthesis.[22] Adipocytes, preadipocytes, and mesenchymal stem cells within fat tissue are the predominant source of aromatase, the enzyme responsible for the conversion of androgens to estrogen.[23,24] Aromatase levels and activity increase as a function of age and adiposity[25,26] and, therefore, contribute to estrogen-induced endometrial proliferation in the postmenopausal woman.[23,27,28] Furthermore, sex hormone–binding globulin (SHBG) levels decrease with increasing adiposity, thereby increasing the pool of bioactive estrogen, even in the absence of de novo estrogen synthesis.[29,30]

Once bound to estrogen receptor-α and/or -β, estrogen directly modulates the transcription of a variety of proproliferative genes including *IGF1R* and *IGF1*.[31-33] G-protein–coupled estrogen receptor 1 (*GPER1*) mediates ligand-dependent nongenomic signaling to stimulate endometrial proliferation via activation of the MAPK and AKT signaling pathways.

Estrogen acts not only as a mitogen, but also as a mutagen. Genotoxic metabolites of estrogen react with DNA to form depurinating adducts, ultimately producing an accumulation of double-stranded DNA breaks and contributing to genetic instability.[34-36] Although the role of estrogen metabolites in the pathogenesis of breast cancer is well characterized, their role in the

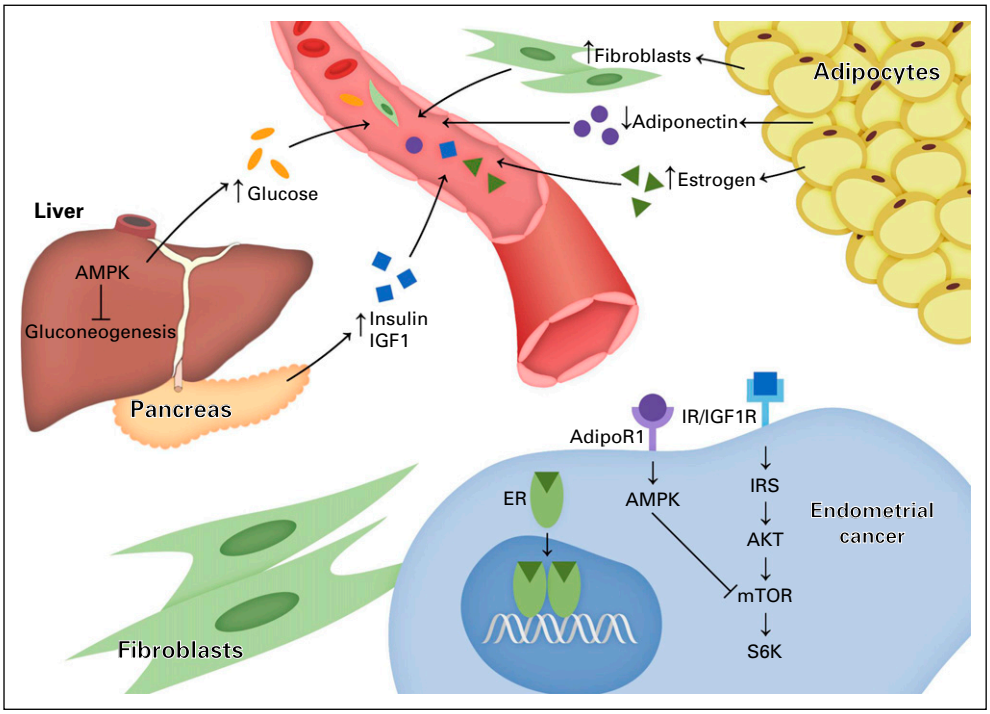

Fig 1. Effects of obesity on endometrial proliferation and tumorigenesis. Obesity contributes to the increased risk of endometrial cancer in the postmenopausal uterus by a variety of mechanisms. Increased adiposity increases aromatase activity, which leads to the conversion of androgens to estrogens, to directly promote endometrial proliferation and transcription of proproliferative genes. The chronic inflammation associated with visceral adiposity is mediated by proinflammatory adipokines and leads to hyperinsulinemia, increases in insulin-like growth factor 1 (IGF1), and hyperglycemia, which fuel endometrial proliferation. A concurrent decrease in anti-inflammatory cytokines is also observed. Inflammation and an increase in estrogen metabolites further contribute to DNA damage and genetic instability. Finally, stem cells can be recruited from adipose tissue, where they contribute to a supportive tumor microenvironment. ER, estrogen receptor; IGF1R, insulin-like growth factor 1 receptor; IR, insulin receptor; IRS, insulin receptor substrate; mTOR, mammalian target of rapamycin. (Illustration created by Suety Kwan).

context of endometrial cancer is not. Approximately a third of endometrial cancers demonstrate DNA mismatch repair defects, as a result of somatic methylation of MLH1 or, less frequently, Lynch syndrome.[37-40] Therefore, localized exposure of the endometrium to estrogen metabolites is more likely to produce genetic mutations contributing to tumorigenesis in the absence of functional DNA repair systems.

Hyperactivity of Insulin and Insulin-Like Growth Factor 1 Signaling in the Endometrium

Type 2 diabetes is characterized by elevated levels of insulin and insulin-like growth factor 1 (IGF1) and hyperglycemia, each of which plays a role in the pathogenesis of endometrial cancer.[41-44] In normal premenopausal women, estrogen-induced cyclic changes in IGF1 expression and signaling modulate endometrial proliferation during the normal menstrual cycle.[45,46] The positive association of endometrial cancer with hyperinsulinemia and type 2 diabetes is well documented.[2,17,44,47,48] Increased expression of insulin and IGF1 receptors is observed in endometrial hyperplasia, which heightens the responsiveness of these cells to insulin and IGF1[46] and promotes hyperactivity of MAPK and PI3K/AKT/mTOR signaling frequently observed in endometrial cancer. Proliferative signaling is further amplified by the loss of the *PTEN* tumor suppressor gene, which acts in opposition to the PI3K/AKT/mTOR pathway and is an early event in the pathogenesis of endometrial cancer. Finally, hyperglycemia, which occurs as consequence of insulin insensitivity, serves to further fuel the growth of metabolically active tissue,[49,50] including endometrial hyperplasia and cancer.

Inflammation and the Role of Adipokines

Adipose tissue is a rich source of secreted polypeptides known as adipokines, which regulate metabolism and modulate the chronic inflammatory state associated with visceral adiposity. Obesity-associated proinflammatory adipokines, such as leptin, interleukin-6, and tumor necrosis factor α, suppress normal insulin signaling and contribute to insulin resistance,[15,48,51] and also promote endometrial proliferation, as previously discussed. Adipokines also regulate the expression of SHBG, thereby influencing systemic levels of bioavailable estrogen. Adiponectin, a potent anti-inflammatory adipokine, induces SHBG synthesis and decreases estrogen bioavailabilty,[29] whereas obesity-induced, proinflammatory cytokines, such as tumor necrosis factor α, are associated with low plasma levels of SHBG and contribute to increased endometrial cancer risk.[52] Furthermore, in the context of adipokine-mediated chronic inflammation, cellular stress is associated with enhanced genetic instability and DNA damage. Mitochondrial reactive oxygen species produced by inflammatory cells can produce DNA strand breaks. Under these conditions, endometrial tissues with DNA mismatch repair defects are likely to accumulate deleterious genetic mutations, leading to endometrial hyperplasia and cancer.

OPPORTUNITIES FOR PREVENTION

Given our knowledge of the pathways involved in obesity-associated endometrial cancer, there are multiple rational interventions for the prevention of endometrial cancer. These include potential lifestyle interventions and surgical procedures that decrease visceral adiposity, as well as medications that aim to interrupt or reverse the hormonal and metabolic derangements associated with obesity and insulin resistance.

Potential Lifestyle Interventions

Public health interventions that decrease the overall prevalence of obesity may have the greatest impact on decreasing endometrial cancer rates in the population. On an individual basis, however, although lifestyle interventions for weight loss may theoretically reduce a woman's risk for developing endometrial cancer, the data to support this are still lacking. There are a limited number of studies evaluating the effect of diet on endometrial cancer risk, and the findings have been mixed at best. Two large meta-analyses have shown that diets with a high glycemic load significantly increase the risk of developing endometrial cancer,[53,54] and a review of three case-control studies suggests that a Mediterranean diet may be associated with a decreased risk of endometrial cancer.[55] However, a recent prospective analysis of participants in the Women's Health Initiative showed that quality of diet (as measured by four diet quality indices) had no impact on the development of endometrial cancer.[56] Two additional analyses examining the healthy eating index (based on the Dietary Guidelines for Americans) and the Recommended Foods Score showed no association between adhering to these diets and developing endometrial cancer.[57,58] There are even fewer studies examining the relationship between exercise and ovarian cancer risk. High-quality prospective studies are needed to better understand the role of these potential lifestyle interventions on the risk of developing ovarian cancer.

Surgical Procedures

Bariatric surgery can lead to dramatic, sustainable weight loss. A recent meta-analysis of six observational studies showed a 60% reduction in the risk of developing endometrial cancer among those who underwent bariatric surgery compared with obese controls (pooled RR, 0.40; 95% CI, 0.20 to 0.79).[59] Among obese women diagnosed with CAH or early-stage endometrial cancer, referral to a bariatric surgeon tends to be well received, with approximately 17% going on to pursue surgical intervention and 59% subsequently attempting weight loss.[60]

Medications

Progestin-based medical therapies counteract the proliferative effect of estrogen on the endometrium. Oral contraceptive pills containing progestins have long been known to be protective against endometrial cancer. A recent meta-analysis of 36 epidemiologic studies demonstrated that for every 5 years women used oral contraceptive pills, there was a 24% reduction in the risk of developing endometrial cancer (RR, 0.76; 95% CI, 0.73 to 0.78; $P < .001$). This effect was durable, persisting for more than 30 years after stopping oral contraceptive use.[61] The use of intrauterine devices (IUDs), including those without embedded progestins, has also been found to be protective, with a 19% decrease in risk among women who have ever used an IUD compared with those who have never used one. The reduction in risk was even

greater when the IUD was used for ≥ 10 years (odds ratio, 0.61; 95% CI, 0.52 to 0.71).[62]

Metformin is another potential chemopreventive medication that is currently under investigation. It increases insulin sensitivity and activates the AMPK pathway, thereby counteracting the PI3K/AKT/mTOR signaling pathway, which promotes endometrial proliferation.[63,64] Additional research is needed before its use in primary chemoprevention.

OBESITY AND THE CLINICAL MANAGEMENT OF ENDOMETRIAL CANCER

Effects of Obesity on Surgical Management

Once diagnosed with endometrial cancer, the effects of obesity can complicate clinical management strategies. The primary treatment of early-stage endometrial cancer involves a total hysterectomy with bilateral salpingo-oophorectomy and often includes lymph node evaluation. Obese patients are often more difficult to operate on than normal-weight counterparts because of technical aspects of the surgery that can be affected by body habitus, such as poor visualization. Obese patients are also more likely to have obesity-related medical comorbidities, which put them at a higher risk of perioperative complications. In a recent systematic review of women undergoing surgery for endometrial cancer, increasing BMI was associated with longer operating times and an increased risk of postoperative morbidity. The total number of surgical complications was highest among morbidly obese patients who underwent laparotomy.[65]

Robotic surgery may offer advantages over traditional laparoscopy in this patient population. One prospective study of obese women undergoing minimally invasive surgery for endometrial cancer demonstrated lower rates of conversion to laparotomy, shorter operative times, increased lymph node retrieval, and shorter hospital stays with robotic surgery compared with laparoscopy.[66]

It is estimated that approximately 10% of patients with early-stage endometrial cancer are medically inoperable as a result of obesity-related medical comorbidities, such as cardiovascular disease and diabetes-related end-organ damage.[67] These patients can be managed with primary radiation therapy. A recent consensus statement from the American Brachytherapy Society recommends that women with inoperable clinical stage I endometrial cancer undergo imaging with magnetic resonance imaging (MRI). Women with no apparent lymph node involvement or deep myometrial invasion on MRI may be managed with brachytherapy alone. If these factors are present or no MRI imaging is performed, a combined approach with external-beam radiation and brachytherapy should be considered.[68]

Premenopausal Patients With Endometrial Cancer

As obesity among young women continues to increase, oncologists are seeing younger women with endometrial cancer. This impacts clinical management in terms of consideration for ovarian conservation at the time of surgery and the use of fertility-sparing treatments. Multiple studies have suggested that young women with early clinical stage disease can be safely managed with fertility-sparing therapy. A meta-analysis of 34 observational studies including 408 women with endometrial cancer evaluated the safety and efficacy of fertility-sparing treatment. Of these, 386 women had grade 1 tumors and 22 had grade 2 or 3 tumors. In most studies, imaging was performed to evaluate for myometrial invasion or distant disease. Women were treated with hormonal therapies such as oral progestins or the progesterone-releasing IUD. In this meta-analysis, 76.2% of women had regression of their tumors, and after initial regression of endometrial cancer, 40.6% experienced disease relapse. Ten women were diagnosed with at least stage II endometrial cancer after experiencing treatment failure with their initial treatment. Two women died as a result of fertility-sparing treatment, both of whom were found to have synchronous ovarian cancers at the time of recurrence. Twenty-eight percent of women achieved at least one live birth, with 41% using assisted reproductive therapy.[69] From a clinical standpoint, proper patient selection is critical in fertility-sparing management. Preoperative imaging with MRI to rule out tumor invasion of the myometrium as well as rule out a synchronous ovarian tumor is important. Consultation with a reproductive endocrinologist can be helpful, especially given that obese women are frequently anovulatory. Areas of controversy include the use of fertility-sparing treatments in women with grade 2 tumors and the efficacy of oral progestin versus the progestin-releasing IUD. Nevertheless, the use of fertility-sparing treatment for early endometrial cancer is a reasonable option for young obese women who are properly counseled about the benefits and potential risks.

Even for women who no longer desire fertility, there are data to support consideration of ovarian conservation among premenopausal women with endometrial cancer. A retrospective review of the SEER database compared outcomes between premenopausal women with stage I endometrial cancer who had ovarian conservation and women who underwent bilateral salpingo-oophorectomy at the time of hysterectomy. There was no impact of ovarian conservation on cancer-specific survival or all-cause mortality.[70] Despite this evidence, rates of ovarian conservation are relatively low (7.2%).[71]

In conclusion, the obesity epidemic has had a dramatic impact on endometrial cancer incidence in the United States. Oncologists are seeing more young obese women affected by endometrial cancer who desire maintaining future fertility. Among older patients with endometrial cancer, the severity of obesity is becoming worse, with many women having a BMI > 40 kg/m^2 and multiple medical comorbidities. There is a critical need to refine options for conservative, nonsurgical management for both of these groups of women. Our institution is conducting an ongoing clinical trial adding everolimus for women with progestin-refractory endometrial cancer as a strategy for conservative management. Additional strategies should continue to be explored.

The role of weight loss, diet, and exercise to improve disease-specific and overall survival among survivors of endometrial cancer also needs to be better defined. Rigorous studies are needed to guide interventions to improve clinical outcomes for this population.

Ultimately, there needs to be greater public awareness about the association between obesity and endometrial cancer. Public health efforts involving education and obesity prevention are critical to improving outcomes for patients with endometrial cancer in the years ahead.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Reeves GK, Pirie K, Beral V, et al: Cancer incidence and mortality in relation to body mass index in the Million Women Study: Cohort study. BMJ 335: 1134, 2007
2. Calle EE, Kaaks R: Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. Nat Rev Cancer 4:579-591, 2004
3. Renehan AG, Tyson M, Egger M, et al: Body-mass index and incidence of cancer: A systematic review and meta-analysis of prospective observational studies. Lancet 371:569-578, 2008
4. World Cancer Research Fund/American Institute for Cancer Research: Continuous Update Project Report. Food: Nutrition, Physical Activity, and the Prevention of Endometrial Cancer. 2013. http://www.dietandcancerreport.org
5. McCullough ML, Patel AV, Patel R, et al: Body mass and endometrial cancer risk by hormone replacement therapy and cancer subtype. Cancer Epidemiol Biomarkers Prev 17:73-79, 2008
6. Calle EE, Rodriguez C, Walker-Thurmond K, et al: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 348:1625-1638, 2003
7. von Gruenigen VE, Tian C, Frasure H, et al: Treatment effects, disease recurrence, and survival in obese women with early endometrial carcinoma: A Gynecologic Oncology Group study. Cancer 107: 2786-2791, 2006
8. Flegal KM, Kruszon-Moran D, Carroll MD, et al: Trends in obesity among adults in the United States, 2005 to 2014. JAMA 315:2284-2291, 2016
9. Sheikh MA, Althouse AD, Freese KE, et al: USA endometrial cancer projections to 2030: Should we be concerned? Future Oncol 10:2561-2568, 2014
10. Soliman PT, Bassett RL, Jr, Wilson EB, et al: Limited public knowledge of obesity and endometrial cancer risk: What women know. Obstet Gynecol 112:835-842, 2008
11. Beavis AL, Cheema S, Holschneider CH, et al: Almost half of women with endometrial cancer or hyperplasia do not know that obesity affects their cancer risk. Gynecol Oncol Rep 13:71-75, 2015
12. Clark LH, Ko EM, Kernodle A, et al: Endometrial cancer survivors' perceptions of provider obesity counseling and attempted behavior change: Are we seizing the moment? Int J Gynecol Cancer 26:318-324, 2016
13. World Cancer Research Fund/American Institute for Cancer Research: Continuous Update Project Report: Food, Nutrition, Physical Activity, and the Prevention of Ovarian Cancer 2014. http://www.dietandcancerreport.org/cup/cup_resources.php
14. Delort L, Kwiatkowski F, Chalabi N, et al: Central adiposity as a major risk factor of ovarian cancer. Anticancer Res 29:5229-5234, 2009
15. Renehan AG, Zwahlen M, Egger M: Adiposity and cancer risk: New mechanistic insights from epidemiology. Nat Rev Cancer 15:484-498, 2015
16. Allott EH, Hursting SD: Obesity and cancer: Mechanistic insights from transdisciplinary studies. Endocr Relat Cancer 22:R365-R386, 2015
17. Park J, Morley TS, Kim M, et al: Obesity and cancer: Mechanisms underlying tumour progression and recurrence. Nat Rev Endocrinol 10:455-465, 2014
18. Khandekar MJ, Cohen P, Spiegelman BM: Molecular mechanisms of cancer development in obesity. Nat Rev Cancer 11:886-895, 2011
19. Klopp AH, Zhang Y, Solley T, et al: Omental adipose tissue-derived stromal cells promote vascularization and growth of endometrial tumors. Clin Cancer Res 18:771-782, 2012
20. Pope BD, Warren CR, Parker KK, et al: Microenvironmental control of adipocyte fate and function. Trends Cell Biol 26:745-755, 2016
21. Mihm M, Gangooly S, Muttukrishna S: The normal menstrual cycle in women. Anim Reprod Sci 124:229-236, 2011
22. Davis SR, Lambrinoudaki I, Lumsden M, et al: Menopause. Nat Rev Dis Primers 1:15004, 2015
23. Blakemore J, Naftolin F: Aromatase: Contributions to physiology and disease in women and men. Physiology (Bethesda) 31:258-269, 2016
24. O'Connor KA, Ferrell RJ, Brindle E, et al: Total and unopposed estrogen exposure across stages of the transition to menopause. Cancer Epidemiol Biomarkers Prev 18:828-836, 2009
25. Simpson ER, Mendelson CR: Effect of aging and obesity on aromatase activity of human adipose cells. Am J Clin Nutr 45:290-295, 1987 (suppl 1)
26. Bulun SE, Simpson ER: Regulation of aromatase expression in human tissues. Breast Cancer Res Treat 30:19-29, 1994
27. Vicennati V, Garelli S, Rinaldi E, et al: Obesity-related proliferative diseases: The interaction between adipose tissue and estrogens in post-menopausal women. Horm Mol Biol Clin Investig 21:75-87, 2015
28. Zhao H, Zhou L, Shangguan AJ, et al: Aromatase expression and regulation in breast and endometrial cancer. J Mol Endocrinol 57:R19-R33, 2016
29. Simó R, Sáez-López C, Barbosa-Desongles A, et al: Novel insights in SHBG regulation and clinical implications. Trends Endocrinol Metab 26:376-383, 2015
30. Simó R, Saez-Lopez C, Lecube A, et al: Adiponectin upregulates SHBG production: Molecular mechanisms and potential implications. Endocrinology 155:2820-2830, 2014
31. Deng L, Feng J, Broaddus RR: The novel estrogen-induced gene EIG121 regulates autophagy and promotes cell survival under stress. Cell Death Dis 1:e32, 2010
32. Westin SN, Broaddus RR, Deng L, et al: Molecular clustering of endometrial carcinoma based on estrogen-induced gene expression. Cancer Biol Ther 8:2126-2135, 2009
33. Thomas C, Gustafsson JA: The different roles of ER subtypes in cancer biology and therapy. Nat Rev Cancer 11:597-608, 2011
34. Cavalieri E, Chakravarti D, Guttenplan J, et al: Catechol estrogen quinones as initiators of breast and other human cancers: Implications for biomarkers of susceptibility and cancer prevention. Biochim Biophys Acta 1766:63-78, 2006
35. Cavalieri E, Rogan E: The molecular etiology and prevention of estrogen-initiated cancers: Ockham's Razor: Pluralitas non est ponenda sine necessitate. Plurality should not be posited without necessity. Mol Aspects Med 36:1-55, 2014
36. Cavalieri EL, Rogan EG: Depurinating estrogen-DNA adducts, generators of cancer initiation: Their minimization leads to cancer prevention. Clin Transl Med 5:12, 2016
37. Meyer LA, Broaddus RR, Lu KH: Endometrial cancer and Lynch syndrome: Clinical and pathologic considerations. Cancer Contr 16:14-22, 2009
38. Batte BA, Bruegl AS, Daniels MS, et al: Consequences of universal MSI/IHC in screening endometrial cancer patients for Lynch syndrome. Gynecol Oncol 134:319-325, 2014
39. Tafe LJ, Riggs ER, Tsongalis GJ: Lynch syndrome presenting as endometrial cancer. Clin Chem 60:111-121, 2014
40. Mills AM, Longacre TA: Lynch syndrome: Female genital tract cancer diagnosis and screening. Surg Pathol Clin 9:201-214, 2016
41. DeFronzo RA, Ferrannini E, Groop L, et al: Type 2 diabetes mellitus. Nat Rev Dis Primers 1: 15019, 2015
42. Vrachnis N, Iavazzo C, Iliodromiti Z, et al: Diabetes mellitus and gynecologic cancer: Molecular mechanisms, epidemiological, clinical and prognostic perspectives. Arch Gynecol Obstet 293:239-246, 2016
43. Poloz Y, Stambolic V: Obesity and cancer, a case for insulin signaling. Cell Death Dis 6:e2037, 2015
44. Nead KT, Sharp SJ, Thompson DJ, et al: Evidence of a causal association between insulinemia and endometrial cancer: A Mendelian randomization analysis. J Natl Cancer Inst 107:djv178, 2015
45. McCampbell AS, Walker CL, Broaddus RR, et al: Developmental reprogramming of IGF signaling and susceptibility to endometrial hyperplasia in the rat. Lab Invest 88:615-626, 2008
46. McCampbell AS, Broaddus RR, Loose DS, et al: Overexpression of the insulin-like growth factor I receptor and activation of the AKT pathway in hyperplastic endometrium. Clin Cancer Res 12: 6373-6378, 2006
47. Lees B, Leath CA, III: The impact of diabetes on gynecologic cancer: Current status and future directions. Curr Obstet Gynecol Rep 4:234-239, 2015
48. Mu N, Zhu Y, Wang Y, et al: Insulin resistance: A significant risk factor of endometrial cancer. Gynecol Oncol 125:751-757, 2012
49. Masur K, Vetter C, Hinz A, et al: Diabetogenic glucose and insulin concentrations modulate transcriptome and protein levels involved in tumour cell migration, adhesion and proliferation. Br J Cancer 104:345-352, 2011
50. Ryu TY, Park J, Scherer PE: Hyperglycemia as a risk factor for cancer progression. Diabetes Metab J 38:330-336, 2014

51. Kwon H, Pessin JE: Adipokines mediate inflammation and insulin resistance. Front Endocrinol (Lausanne) 4:71, 2013

52. Simó R, Barbosa-Desongles A, Sáez-Lopez C, et al: Molecular mechanism of TNFα-induced downregulation of SHBG expression. Mol Endocrinol 26: 438-446, 2012

53. Mulholland HG, Murray LJ, Cardwell CR, et al: Dietary glycaemic index, glycaemic load and breast cancer risk: A systematic review and meta-analysis. Br J Cancer 99:1170-1175, 2008

54. Nagle CM, Olsen CM, Ibiebele TI, et al: Glycemic index, glycemic load and endometrial cancer risk: Results from the Australian National Endometrial Cancer study and an updated systematic review and meta-analysis. Eur J Nutr 52:705-715, 2013

55. Filomeno M, Bosetti C, Bidoli E, et al: Mediterranean diet and risk of endometrial cancer: A pooled analysis of three Italian case-control studies. Br J Cancer 112:1816-1821, 2015

56. George SM, Ballard R, Shikany JM, et al: A prospective analysis of diet quality and endometrial cancer among 84,415 postmenopausal women in the Women's Health Initiative. Ann Epidemiol 25:788-793, 2015

57. Chandran U, Bandera EV, Williams-King MG, et al: Adherence to the dietary guidelines for Americans and endometrial cancer risk. Cancer Causes Control 21:1895-1904, 2010

58. Mai V, Kant AK, Flood A, et al: Diet quality and subsequent cancer incidence and mortality in a prospective cohort of women. Int J Epidemiol 34:54-60, 2005

59. Upala S, Sanguankeo A: Bariatric surgery reduces risk of endometrial cancer. Surg Obes Relat Dis 11:1410, 2015

60. Jernigan AM, Maurer KA, Cooper K, et al: Referring survivors of endometrial cancer and complex atypical hyperplasia to bariatric specialists: A prospective cohort study. Am J Obstet Gynecol 213: 350.e1-10, 2015

61. Collaborative Group on Epidemiological Studies on Endometrial Cancer: Endometrial cancer and oral contraceptives: An individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Lancet Oncol 16:1061-1070, 2015

62. Felix AS, Gaudet MM, La Vecchia C, et al: Intrauterine devices and endometrial cancer risk: A pooled analysis of the Epidemiology of Endometrial Cancer Consortium. Int J Cancer 136:E410-E422, 2015

63. Zhou G, Myers R, Li Y, et al: Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 108:1167-1174, 2001

64. Jalving M, Gietema JA, Lefrandt JD, et al: Metformin: Taking away the candy for cancer? Eur J Cancer 46:2369-2380, 2010

65. Bouwman F, Smits A, Lopes A, et al: The impact of BMI on surgical complications and outcomes in endometrial cancer surgery: An institutional study and systematic review of the literature. Gynecol Oncol 139:369-376, 2015

66. Gehrig PA, Cantrell LA, Shafer A, et al: What is the optimal minimally invasive surgical procedure for endometrial cancer staging in the obese and morbidly obese woman? Gynecol Oncol 111:41-45, 2008

67. Acharya S, Esthappan J, Badiyan S, et al: Medically inoperable endometrial cancer in patients with a high body mass index (BMI): Patterns of failure after 3-D image-based high dose rate (HDR) brachytherapy. Radiother Oncol 118:167-172, 2016

68. Schwarz JK, Beriwal S, Esthappan J, et al: Consensus statement for brachytherapy for the treatment of medically inoperable endometrial cancer. Brachytherapy 14:587-599, 2015

69. Gallos ID, Yap J, Rajkhowa M, et al: Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: A systematic review and metaanalysis. Am J Obstet Gynecol 207: 266.e1-12, 2012

70. Wright JD, Buck AM, Shah M, et al: Safety of ovarian preservation in premenopausal women with endometrial cancer. J Clin Oncol 27:1214-1219, 2009

71. Wright JD, Jorge S, Tergas AI, et al: Utilization and outcomes of ovarian conservation in premenopausal women with endometrial cancer. Obstet Gynecol 127:101-108, 2016

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Addressing the Role of Obesity in Endometrial Cancer Risk, Prevention, and Treatment

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No relationship to disclose

Rosemarie E. Schmandt
No relationship to disclose

Karen H. Lu
No relationship to disclose