

Prevention of endometrial cancer with a healthier lifestyle: A review of the literature and proposal of the I.M.P.R.O.V.E. strategy

Del Pup L^{1*}, Buonomo B² and Peccatori FA²

¹Gynecology Specialist, University Sanitary Agency Friuli Central (ASU FC), Udine, Italy

²Fertility and Procreation Unit, Division of Gynecologic Oncology, European Institute of Oncology IRCCS, Milan, Italy

Abstract

Type I endometrial cancer is mainly associated with obesity, chronic hyperinsulinemia and insulin resistance. Thus, improving lifestyle should be a main goal of primary prevention for this neoplasm. Nonetheless, patients adherence to a healthy lifestyle (playing sports, weight control, balanced diet, etc.) is generally insufficient. The aim of this paper is to provide a review of the available literature about the correlation between endometrial cancer and lifestyle. Then, a novel strategy of counseling is proposed; this approach, based both on evidence-based medicine and clinical psychology, can be easily remembered with the acronym I.M.P.R.O.V.E. (Inform, Motivate, Prescribe, Reward, Oversee, Visualize, Empower).

Background

Endometrial cancer (EC) is the most common type of gynecologic cancer in developed countries [1,2]. Even if molecular analysis is now used to identify different subsets of EC [3], it has been traditionally classified into two histological types that differ in incidence, estrogen responsiveness and prognosis [4]. Type I EC has a well-recognized precursor lesion, atypical hyperplasia (AH), and is the most common one. Usually, it is a low-grade, low-stage, estrogen-dependent tumor that is associated with obesity and a better outcome. By contrast, type II tumors are relatively rare, high-grade, clinically aggressive neoplasms; they are more frequent in non-obese women and estrogen-independent [5]. The rising incidence of type I EC is related to the worldwide spread of obesity and obesity-related hyperinsulinemia, that are associated with more than 80% of the diagnoses [6,7]. Hyperinsulinemia and insulin resistance (IR) increase bioavailability of steroid hormones and local inflammation; these factors could be promoters of tumorigenesis and tumor progression [8].

Considering the strong correlation between type I EC and lifestyle, a behavioral intervention mainly based on physical activity and healthy eating could effectively impact the risk of developing this tumor, prevent its recurrence and improve patients' quality of life (QoL) [9,10].

Unfortunately, patients' adherence to healthy lifestyles seems to be insufficient and poorly studied. The aim of this paper is to provide a review of the current available literature about this topic in order to offer healthcare providers (HCPs) some practical tools for patients counselling in the setting of primary prevention of type I EC.

Methods

We performed a narrative review of the literature on PubMed (Medline), with restriction to publications in English, using the following keywords: endometrial neoplasms, prevention, lifestyle,

insulin resistance. There were no limits placed on time of publication. According to the analysis of the available data, a novel counseling approach is proposed to improve the strategies of EC primary prevention.

Review of the literature

Currently, given the emerging epidemic of EC because of the increase of obesity and sedentary life, lifestyle changes are urgently needed to reduce incidence and recurrences [10].

For every 5 kg/m² increase in Body Mass Index (BMI), there is a 60% increased risk of EC, with a BMI above 25 kg/m² the risk is doubled and with a BMI above 30 kg/m² the risk is tripled [11,12]. Type 2 diabetes mellitus (DM) is also a strong risk factor for benign endometrial polyps, AH and type I EC [13-15]. Large epidemiological studies adjusting for BMI, conclude that type 2 DM confers a 62% increased risk of EC, independent of obesity [16,17]. Hence, obesity and IR play synergistically a critical role in EC pathogenesis [18-20]. Using data collected within the European Prospective Investigation into Cancer and Nutrition (EPIC), Dossus *et al.* confirmed that IR is one of the main pathogenetic factor for EC and that it is strongly related to obesity [21]. Significantly higher levels of fasting insulin and non-fasting C peptide were reported in patients diagnosed with EC [22]. Insulin can increase tumor growth by binding to the insulin receptor or the insulin-like growth factor 1 (IGF-1) receptor, which

*Correspondence to: Lino Del Pup, University Sanitary Agency Friuli Central (ASU FC), Via San Valentino, 18 Udine (UD), Italy, Tel:+39 3386672444, E-mail: info@delpupginecologia.it

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are both increased in EC [23]. Insulin also down-regulates the most important IGF binding protein (IGFBP) within the endometrium, IGFBP-1, and thus increases bioavailability of IGF-1 within the tissue, stimulating further tumor development [24]. An indirect mechanism of action of insulin on endometrial carcinogenesis is an increase in levels of bioavailable estrogens, through a decrease in the hepatic synthesis of sex hormone-binding globulin (SHBG) [25]. Moreover, IR and hyperinsulinemia, as in metabolic syndrome, stimulate the ovarian and adrenal cortex production of androgens, mostly androstenedione and testosterone. These are metabolized into estrogen from the aromatase enzymes in adipose tissue. Contrary to estrogens, androgens themselves do not seem to stimulate endometrial cell proliferation [26].

There is a growing body of evidence supporting metformin as a potential anti-cancer agent, and data that propose its use to reduce the risk of EC through hyperinsulinemia and IR reduction [27]. Metformin may assist in the reversal of AH to a normal endometrial histology, in the reduction of cell proliferation biomarkers implicated in tumor progression, and in the improvement of overall survival in EC [28]. Thus, metformin could be considered as an experimental integration treatment where lifestyle improvement is not achieved or not sufficient.

Women affected by polycystic ovary syndrome (PCOS) represent a unique combination of some of the main predisposing factors to EC. Insulin resistance and anovulatory cycles cause a hyperestrogenic state, which is associated to a EC lifetime risk of 9% [20]. Progesterone has a protective effect as it counteracts the mitogenic effects of estrogen by increasing synthesis of IGFBP-1; thus, it reduces the excess of IGF-1 and it promotes expression of the estrogen sulfotransferase and 17 β -hydroxysteroid dehydrogenase (17 β -HSD), that transform estradiol into the less powerful estrone. A relative deficiency of progesterone like in PCOS appears to be a more important risk factor for EC than excessive estrogens.

Adiponectin and IGFBPs regulate glucose levels and insulin sensitivity and are protective factors against EC development. They are reduced in individuals affected by obesity and hyperinsulinemia: for each 5 μ g/mL decrease in adiponectin levels, the risk of EC has been found to increase by 18% [29].

Hypothyroidism is also related to EC risk factors and it is a negative prognostic factor for EC [30].

Dossus *et al.* also demonstrated an additional role for chronic inflammation, that is a common feature of obesity [21]: inflammation may result in DNA damage through free radical formation and defective immunosurveillance, facilitating tumorigenesis [31]. Noteworthy, aspirin (ASA) and other nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to inhibit endometrial cancer cell growth in vitro through the induction of apoptosis in a dose- and time-dependent manner. Consistent with data from colon [32] and other cancer cell lines, these data suggest that NSAIDs exert their anticancer effects through both COX-2-dependent and COX-2-independent mechanisms [33].

EC patients generally have unhealthy lifestyles with reduced physical activity, abdominal obesity (93%), poor eating habits, high glucose levels and more comorbidities [34,35]. A sedentary lifestyle and a high BMI are also highly correlated with an increased risk of death from EC [36]. EC patients with a BMI is > 35 kg/m² have a two-fold increased mortality risk. More than 7 hours of moderate to vigorous physical activity per week prior to a diagnosis had a 43% lower risk of 5-year all-cause mortality, when compared with women who never/

rarely exercised [36]. On the contrary, Seidelin *et al.* showed that a sedentary behavior could be more damaging than being overweight [37]. Physical activity is associated with a 38% to 46% relative reduction in EC risk [38-42]. According to a meta-analysis [43] women who were inactive and who sat for 9 hours per day had a two-fold risk of EC compared with active women who sat fewer than 3 hours per day (RR 2.14; 95% CI, 1.48-3.10).

Moreover, it's well known that adopting a healthy lifestyle reduces by 29% the incidence of any cancer (HR 0.71 CI 0.66-0.76; 16 studies with 1.9 million participants) and by 52% cancer mortality (HR 0.48 CI 0.42-0.54; 30 studies with 1.8 million participants) [44]. A healthy lifestyle reduces any hormone sensitive cancer risk: breast, endometrial and ovarian [45] and it also decreases thromboembolic risk.

Vitamin D supplements do not reduce EC risk [46], as reported for ovarian cancer [45].

Smokers have a reduced risk of endometrial cancer in prospective (RR, 0.81; 95% CI, 0.74-0.88) and case-control studies (odds ratio, 0.72; 95% CI, 0.66-0.79) studies [47].

One cup of caffeinated coffee per day is associated with a 7% reduction in endometrial cancer risk (RR 0.93, 95% CI 0.89-0.97), compared with a 4% risk reduction with one cup of decaffeinated coffee/day (RR 0.96, 95% CI 0.92-0.99) [48].

Hormonal contraception (HC) is the main pharmacological way to reduce EC risk, taking advantage of the same protective mechanism of pregnancy. The risk reduction is proportionate to the duration of HC assumption and its protective effect persists more than 30 years after last use [49].

Fertility treatments do not seem to affect EC risk, while they help achieving a pregnancy and allow breastfeeding that significantly decrease EC risk [50]. Healthy lifestyle improves fertility mostly in obese, insulin resistant patients and it is first line non-pharmacological treatment of infertility in PCOS [51].

Recently, Njoku *et al.* tried to identify specific groups of women at a particularly high risk of EC for whom risk-reducing interventions are likely to have a significant impact. They also concluded that bariatric surgery, the administration of cyclic hormones (PCOS), the use of Levonorgestrel-releasing intrauterine system (LNG-IUS) (fertility-sparing treatment of AH) are proven methods of EC prevention in high-risk women, while non-surgical weight loss and modulation of insulin resistance with metformin are potential methods of prevention that require further evidence [52]. In fact, we have few evidence that lifestyle-based weight loss is enough to reduce EC risk, maybe just because of self-reporting and paucity of weight reduction. On the other hand, bariatric surgery, that achieves a more substantial weight loss, significantly decreases EC risk (HR, 0.56; 95% CI, 0.35-0.89) but with possible short-term surgical complications and long-term risks [53].

Discussion and new strategies

EC is highly influenced by IR, inactivity and obesity. That explains why it is so frequent nowadays, but also highly preventable [10].

A healthy lifestyle is really important for EC primary prevention: a recent Canadian study reported a 5% reduction in EC for every unit increase of the Healthy Lifestyle Index (HLI) risk [54].

Adherence to these behavioral indications is generally insufficient and hard to quantify. Psychological factors can reduce the accuracy of self-reporting, such as limited recall, denial, deliberate fabrication,

and socially desirable responding to providers what the provider wants to hear. This generates methodological problems to demonstrate its efficacy. Moreover, there are also many confounding factors, like smoking, coffee, pregnancies, contraception, aspirin or metformin administration.

A key point that have to be stressed is that adherence to lifestyle changes and their effectiveness mainly depend on how HCPs propose them. Lifestyle counseling is very important, but in order to be effective it requires substantial and long-term patient engagement difficult to achieve in the setting of primary prevention.

In order to overcome these critical issues, a novel strategy of counseling is proposed; this approach gets ideas from both evidence-based medicine and clinical psychology, and it can be easily remembered with the acronym I.M.P.R.O.V.E. (Inform, Motivate, Prescribe, Reward, Oversee, Visualize, Empower).

Inform

Informing patients that EC and its recurrences can be prevented by changing lifestyle. Clark *et al.* showed that EC patients were most likely to make lifestyle modifications after an adequate counseling by a physician. Unfortunately, only 29% of them reported to have received clear information about the relationship between obesity and EC [55].

Information should be the first step to approach the higher risk populations for primary prevention and every EC patient during follow up to prevent possible recurrences.

In order to obtain a sort of “informed consent” to the prescription, HCPs have the duty to make patient aware of the main risk factors for EC and of their deep relationship with lifestyle behaviors.

Moreover, many of these conditions (i.e. PCOS, overweight, obesity, hyperinsulinemia, IR, type 2 DM and hypothyroidism) are not only associated with a higher risk of EC, but also with cardiovascular diseases (CVDs) and other tumors. Ward *et al.* reported that CVD is the main cause of mortality at 10 years post EC diagnosis [56].

Thus, a multidisciplinary team should involve several specialties like Ob/Gyn, primary care physicians, diabetologists, dietitians, cardiologists, oncologists and psychologists. These different figures should ideally be vehicles of coordinated messages [57]. A practical example could be patients diagnosed with PCOS because they typically have multiple contacts with Ob/Gyn since young age and lifestyle advice for PCOS treatment are the same as that for EC prevention [20].

Motivate

Trying to find reasons to change lifestyle that are relevant for that specific patient.

Adherence will be optimal only if there is a strong and clear motivation. HCPs have to listen actively and nonjudgmentally, avoiding assumptions and trying to understand the patient’s perspective in order to activate her intrinsic motivation.

Patients’ peculiar beliefs and interpretations about their risk are surprisingly different from the physicians’ perspective. They depend both on personal knowledge and how the risk is shown, as relative risk or absolute numbers. Furthermore, they are influenced by the subjective cognitive interpretation and the emotional impact of that risk. Emotional reasons are stronger motivations than actual risk. As an example, if a relative or a friend is affected by EC, this is felt as a stronger motivation to adhere to primary prevention strategies.

Hence, the best way to motivate patients is stressing issues perceived as more concrete and tangible in their daily life: for example, in the collective image, CVD related to obesity and IR motivate to change lifestyle more than cancer.

Prescribe

Prescribing personalized and measurable behavioral advices.

The first advice is to increase physical activity considering that sedentary lifestyle is an independent risk factor for EC [37].

The second advice is to adapt caloric intake in order to normalize body weight. This intervention is mainly effective in adolescents and young adults considering that for each 5 kg increase in weight over the time period from 18 years to adulthood, the risk of EC is increased by 18% (95% CI, 15%–21%) [58]. A useful suggestion could be reducing simple carbohydrates to fight hyperinsulinemia and IR, even if there is no strong evidence about an established association between reduced risk of EC and a specific diet [59]. Ketogenic diet (KD) is a low-carbohydrate, high-fat diet based on the “Warburg effect” principle: cancer cells metabolism depends on aerobic glycolysis for fuel acquisition. Unlike normal cells, most types of cancer cells are unable to metabolize ketones. Thus, KD objective is to “starve” cancer cells of the glucose and insulin required for proliferation. Cohen *et al.* reported that KD in EC patients, does not negatively affect QoL and it may improve physical function, increase energy and diminish specific food cravings [60]. Moreover, increasing coffee consumption by four cups per day seems to be associated with a 20% reduction in EC relative risk (RR 0.80; 95% CI 0.72 to 0.89) and with a 24% reduction in postmenopausal EC risk (RR 0.76; 95% CI 0.69 to 0.83) [61].

The suggested changes should be achievable and realistic. It is not effective and controllable to give the usual generic indications, like “exercise more” and “lose weight”. These goals should be more effectively reached by using strategies that take into account the interests and habits of every single patient to prescribe a tailored and suitable behavioral program.

Reward

Rewarding the restrictions prescribed with satisfactory activities based on women’ preference.

Patients can not feel an immediate benefit from lifestyle advices. Indeed, they only feel the downsides at first: pain and fatigue after physical activity, renounces, less diet satisfaction. It is unrealistic to expect adherence to prescription without any short-term perception of benefit and pleasure. Exercise should be done encouraging patients to do just those activities that they prefer; it is important to inquire about what is satisfying for the individual (es dancing, group sports, etc.). Well-accepted activities improve QoL and they counterbalance efforts and renounces. Group activities should be preferred as they give positive social support. When a restriction of the caloric intake is prescribed, any improvement of taste should be advised counterbalancing the reduced pleasure of eating a lot.

A reward could be only psychological, as the satisfaction doing something good or approved by others. Anyway, patients have to understand that those activities are not just for pleasure, but a real medical prescription. The time and resources dedicated to hobbies or sports do not mean a less dedication to work and family, but they are part of a cure. Thus, they should not feel guilty or selfish if they do

something pleasurable. They must feel that they are investing in health and sparing health care resources.

Patient should complete this first part of I.M.P.R.O.V.E. counseling (inform, motivate, prescribe, reward) going out with a positive message of doing something that makes them happier. It's better to focus on performing pleasurable activities than to be worried only about their immediate impact on EC risk.

Oversee

Supervising patients' adherence to medical provisions can be done by scheduling a check up after 3 to 6 months according to individual needs or medical protocols. This follow-up may be face-to-face or also by phone or e-mails. If patients are left alone, their compliance is generally insufficient.

A randomized controlled trial (RCT) about the impact of structured lifestyle changes on EC survivors showed that only 30% of participants succeeded in the weight reduction goal [62]. If adherence is suboptimal, the first part of I.M.P.R.O.V.E. strategic counselling (inform, motivate, prescribe, reward) should be used again.

Visualize

Visualizing measurable changes during follow up in order to give a positive feedback and to reinforce motivation and compliance. If patients do not see any tangible change, they feel only the efforts and the renounces without satisfaction. Evidence of any change could be visualized in a strategic way to be better understood according to the educational level.

Self-monitoring devices, fitness tracking technologies or step counters, waist circumference and impedance measurements could be used as visual proofs of physical improvement.

Also histograms can help more than only verbalizing results.

Empower

Empowering to reinforce and keep adherence lifetime.

Women should feel they are not the passive victims of EC, but they have the power to reduce the risk [62]. At the end of consultation, they should feel the satisfaction to be owners of their destiny.

Conclusion

EC is the most common gynaecologic malignancy and its incidence is increasing all around the world because of the growing prevalence of obesity. Effective risk-reducing interventions targeting the key mechanisms that drive endometrial carcinogenesis may reduce EC incidence, particularly when aimed at those at greatest risk. An understanding of the key risk factors and their role in cancerogenesis is critical in developing such prevention strategies. This paper summarizes the major risk factors for EC and the evidence for available risk-reducing interventions in high-risk women. A novel counseling approach is proposed, named I.M.P.R.O.V.E. (Inform, Motivate, Prescribe, Reward, Oversee, Visualize, Empower). This strategy helps patients to change their lifestyle in the setting of primary prevention of EC, using simple tools, based on an integration between scientific evidences and clinical psychology. Further research is needed to clarify the role of possible confounders on endometrial tumorigenesis and to validate this innovative approach also in other fields rather than EC prevention.

Competing interests

The authors declare that they have no conflict of interest. No funding was received for this specific research.

Authors' contributions

All authors listed have contributed sufficiently in the writing and/or critically revising of the paper; they have approved the submitted final version.

References

- Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, et al. (2005) Endometrial cancer. *Lancet* 366: 491-505. [Crossref]
- Sankaranarayanan R, Ferlay J (2006) Worldwide burden of gynaecological cancer: The size of the problem. *Best Pract Res Clin Obstet Gynaecol* 20: 207-225.
- Kommos S, McConechy MK, Kommos F, Leung S, Bunz A, et al. (2018) Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series. *Ann Oncol* 29: 1180-1188.
- Bokhman JV (1983) Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol* 15: 10e7.
- Suarez AA, Felix AS, Cohn DE (2017) Bokhman redux: endometrial cancer "types" in the 21st century. *Gynecol Oncol* 144: 243e9.
- Arthur RS, Kabat GC, Kim MY, Wild RA, Shadyab AH, et al. (2019) Metabolic syndrome and risk of endometrial cancer in postmenopausal women: a prospective study. *Cancer Causes Control* 30: 355-363.
- Nevadunsky NS, Van Arsdale A, Strickler HD, Moadel A, Kaur G, et al. (2014) Obesity and age at diagnosis of endometrial cancer. *Obstet Gynecol* 124: 300-306. [Crossref]
- Calle EE, Kaaks R (2004) Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 4: 579-591.
- Koutoukidis DA, Beeken RJ, Manchanda R, Burnell M, Ziauddeen N, et al. (2019) Diet, physical activity, and health-related outcomes of endometrial cancer survivors in a behavioral lifestyle program: the Diet and Exercise in Uterine Cancer Survivors (DEUS) parallel randomized controlled pilot trial. *Int J Gynecol Cancer* 29: 531-540.
- Moore K, Brewer MA (2017) Endometrial Cancer: Is This a New Disease? *Am Soc Clin Oncol Educ Book* 37: 435-442. [Crossref]
- Crosbie EJ, Zwahlen M, Kitchener HC, Egger M, Renehan AG (2010) Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 19: 3119-3130.
- Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M (2008) Body mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 371: 569e78.
- Bueloni-Dias FN, Spadoto-Dias D, Delmanto LR, Nahas-Neto J, Nahas EA (2016) Metabolic syndrome as a predictor of endometrial polyps in postmenopausal women. *Menopause* 23: 759-764. [Crossref]
- Kaya S, Kaya B, Keskin HL, Kayhan Tetik B, Yavuz FA (2019) Is there any relationship between benign endometrial pathologies and metabolic status? *J Obstet Gynaecol* 39: 176-183. [Crossref]
- Kitson SJ, Maskell Z, Sivalingam VN, Allen JL, Ali S, et al. (2019) PRE-surgical metformin in uterine malignancy (PREMIUM): a multi-center, randomized double-blind, placebo-controlled phase III trial. *Clin Canc Res* 25: 2424e32.
- Barone BB, Yeh HC, Snyder CF (2008) Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA* 300: 2754-2764.
- Saed L, Varse F, Baradaran HR, Moradi Y, Khateri S, et al. (2019) The effect of diabetes on the risk of endometrial Cancer: an updated a systematic review and meta-analysis. *BMC Canc* 19: 527.
- Kaaks R, Lukanova A, Kurzer MS (2002) Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiol Biomarkers Prev* 11: 1531-1543.
- Gunter MJ, Hoover DR, Yu H (2008) A prospective evaluation of insulin and insulin-like growth factor-I as risk factors for endometrial cancer. *Cancer Epidemiol Biomarkers Prev* 17: 921-929.

20. MacKintosh ML, Crosbie EJ (2018) Prevention strategies in endometrial carcinoma. *Curr Oncol Rep* 20: 101.
21. Dossus L, Lukanova A, Rinaldi S (2013) Hormonal, metabolic, and inflammatory profiles and endometrial cancer risk within the EPIC cohort - a factor analysis. *Am J Epidemiol* 177: 787-799.
22. Hernandez AV, Pasupuleti V, Benites-Zapata VA (2015) Insulin resistance and endometrial cancer risk: a systematic review and meta-analysis. *Eur J Cancer* 51: 2747-2758.
23. Cust AE, Kaaks R, Friedenreich C (2007) Metabolic syndrome, plasma lipid, lipoprotein and glucose levels, and endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Endocr Relat Cancer* 14: 755-767.
24. Bell SC (1991) The insulin-like growth factor binding proteins--the endometrium and decidua. *Ann N Y Acad Sci* 622: 120-137. [Crossref]
25. Franks S, Kiddy DS, Hamilton-Fairley D, Bush A, Sharp PS, et al. (1991) The role of nutrition and insulin in the regulation of sex hormone binding globulin. *J Steroid Biochem Mol Biol* 39: 835-838. [Crossref]
26. Tuckerman EM, Okon MA, Li T (2000) Do androgens have a direct effect on endometrial function? An in vitro study. *Fertil Steril* 74: 771-779.
27. Yang BY, Gulnazi Y, Du Y, Ning CC, Cheng YL, et al. (2020) Metformin plus megestrol acetate compared with MA alone as fertility-sparing treatment in patients with atypical endometrial hyperplasia and well-differentiated endometrial cancer: a randomised controlled trial. *BJOG* 21.
28. Meireles CG, Pereira SA, Valadares LP, Rêgo DF, Simeoni LA, et al. (2017) Effects of metformin on endometrial cancer: Systematic review and meta-analysis. *Gynecol Oncol* 147: 167-180.
29. Schmandt RE, Iglesias DA, Co NN (2011) Understanding obesity and endometrial cancer risk: opportunities for prevention. *Am J Obstet Gynecol* 205: 518-525.
30. Wang Y, Zhou R, Wang J (2019) Relationship between Hypothyroidism and Endometrial Cancer. *Aging Dis* 10: 190-196.
31. Kitson SJ, Evans DG, Crosbie EJ (2017) Identifying high-risk women for endometrial cancer prevention strategies: proposal of an endometrial cancer risk prediction model. *Canc Prev Res* 10: 1e13.
32. Piazza GA, Alberts DS, Hixson LJ, Paranka NS, Li H, et al. (1997) Sulindac sulfone inhibits azoxymethane-induced colon carcinogenesis in rats without reducing prostaglandin levels. *Cancer Res* 57: 2909-2915. [Crossref]
33. Modugno F, Ness RB, Chen C, Weiss NS (2005) Inflammation and endometrial cancer: a hypothesis. *Cancer Epidemiol Biomarkers Prev* 4: 2840-2847.
34. Modesitt SC, Geffel DL, Via J, L Weltman A (2012) Morbidly obese women with and without endometrial cancer: are there differences in measured physical fitness, body composition, or hormones? *Gynecol Oncol* 124: 431-436. [Crossref]
35. von Gruenigen VE, Waggoner SE, Frasure HE, Kavanagh MB, Janata JW, et al. (2011) Lifestyle challenges in endometrial cancer survivorship. *Obstet Gynecol* 117: 93-100. [Crossref]
36. Arem H, Pfeiffer RM, Moore SC (2016) Body mass index, physical activity, and television time in relation to mortality risk among endometrial cancer survivors in the NIH-AARP Diet and Health Study cohort. *Cancer Causes Control* 27: 1403-1409.
37. Seidelin UH, Ibfelt E, Andersen I, Steding-Jessen M (2016) Does stage of cancer, comorbidity or lifestyle factors explain educational differences in survival after endometrial cancer? A cohort study among Danish women diagnosed 2005-2009. *Acta Oncol* 55: 680-685. [Crossref]
38. Moradi T, Weiderpass E, Signorello LB (2000) Physical activity and postmenopausal endometrial cancer risk (Sweden). *Cancer Causes Control* 11: 829-837.
39. PDQ Screening and Prevention Editorial Board (2020) Endometrial Cancer Prevention (PDQ®): Health Professional Version. 2020 Feb 27. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US).
40. Schouten LJ, Goldbohm RA, van den Brandt PA (2004) Anthropometry, physical activity, and endometrial cancer risk: results from the Netherlands Cohort Study. *J Natl Cancer Inst* 96: 1635-1638. [Crossref]
41. Hawley JA, Lessard SJ (2008) Exercise training-induced improvements in insulin action. *Acta Physiol (Oxf)* 192: 127-135.
42. Schmid D, Behrens G, Keimling M, Jochem C, Ricci C, et al. (2015) A systematic review and meta-analysis of physical activity and endometrial cancer risk. *Eur J Epidemiol* 30: 397-412.
43. Moore SC, Gierach GL, Schatzkin A (2010) Physical activity, sedentary behaviours, and the prevention of endometrial cancer. *Br J Cancer* 103: 933-938.
44. Zhang YB, Pan XF, Chen J, Cao A, Zhang YG, et al. (2020) Combined lifestyle factors, incident cancer, and cancer mortality: a systematic review and meta-analysis of prospective cohort studies. *Br J Cancer* 10.
45. Del Pup L, Driul L, Peccatori FA (2020) Lifestyle advice to reduce ovarian cancer risk. *WCRJ* 7: e1466.
46. Zeleniuch-Jacquotte A, Gallicchio L, Hartmuller V (2010) Circulating 25-hydroxyvitamin D and risk of endometrial cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 172: 36-46.
47. Zhou B, Yang L, Sun Q, Cong R, Gu H, et al. (2008) Cigarette smoking and the risk of endometrial cancer: a meta-analysis. *Am J Med* 121: 501-508. [Crossref]
48. Zhou Q, Luo M-L, Li H, Li M, Zhou J-G (2015) Coffee consumption and risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. *Sci Rep* 5: 13410.
49. Collaborative Group on Epidemiological Studies on Endometrial Cancer (2015) Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. *Lancet Oncol* 16: 1061-70.
50. Del Pup L, Peccatori FA, Levi-Setti PE, Codacci-Pisanelli G, Patrizio P (2018) Risk of cancer after assisted reproduction: a review of the available evidences and guidance to fertility counsellors. *European Review for Medical and Pharmacological Sciences* 22: 8042-8059.
51. Costello MF, Misso ML, Balen A, Boyle J, Devoto L (2019) Evidence summaries and recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome: assessment and treatment of infertility. *Hum Reprod Open* 4: 021.
52. Njoku K, Abiola J, Russell J, Crosbie EJ (2019) Endometrial cancer prevention in high-risk women. *Best Pract Res Clin Obstet Gynaecol* 20: S1521-S6934.
53. Schauer DP, Feigelson HS, Koebnick C (2019) Bariatric Surgery and the Risk of Cancer in a Large Multisite Cohort. *Ann Surg* 269: 95-101.
54. Arthur R, Kirsh VA, Kreiger N, Rohan T (2018) A healthy lifestyle index and its association with risk of breast, endometrial, and ovarian cancer among Canadian women. *Cancer Causes Control* 29: 485-493. [Crossref]
55. Clark LH, Ko EM, Kernodle A (2016) Endometrial cancer survivors' perceptions of provider obesity counseling and attempted behavior change: are we seizing the moment? *Int J Gynecol Cancer* 26: 318-324.
56. Ward KK, Shah NR, Saenz CC (2012) Cardiovascular disease is the leading cause of death among endometrial cancer patients. *Gynecol Oncol* 126: 176-179.
57. Koutoukidis DA, Beeken RJ, Lopes S (2016) Attitudes, challenges and needs about diet and physical activity in endometrial cancer survivors: a qualitative study. *Eur J Cancer Care* 21.
58. Aune D, Navarro Rosenblatt DA, Chan DS, Vingeliene S (2015) Anthropometric factors and endometrial cancer risk: a systematic review and dose-response meta-analysis of prospective studies. *Ann Oncol* 26: 1635-48.
59. International Agency for Research On Cancer: IARC Handbooks of Cancer Prevention. Volume 8: Fruit and Vegetables. Lyon, France: International Agency for Research On Cancer, 2003.
60. Cohen CW, Fontaine KR, Arend RC, Soleymani T, Gower BA (2018) Favourable Effects of a ketogenic diet on physical function, perceived energy, and food cravings in women with ovarian or endometrial Cancer: A Randomized, controlled trial. *Nutrients* 30: 10.
61. Lafranconi A, Micek A, Galvano F, Rossetti S, Del Pup L (2017) Coffee decreases the risk of endometrial cancer: A dose-response meta-analysis of prospective cohort studies. *Nutrients* 9: E1223.
62. von Gruenigen V, Frasure H, Kavanagh MB, Janata J, Waggoner S, et al. (2012) Survivors of uterine cancer empowered by exercise and healthy diet (SUCCEED): a randomized controlled trial. *Gynecol Oncol* 125: 699-704. [Crossref]

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