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Review

Cancer Prevention Research

Identifying High-Risk Women for Endometrial Cancer Prevention Strategies: Proposal of an Endometrial Cancer Risk Prediction Model

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Abstract

Already the fourth most common cancer in women in the developed world, the incidence of endometrial cancer is increasing rapidly, in line with the increasing prevalence of obesity. Relatively few studies have been undertaken of risk-reducing interventions aimed at limiting the impact of the disease on both individuals and the health service. Those that have been performed have demonstrated only modest results due to their application in relatively unselected populations. A validated risk prediction model is therefore urgently required to identify individuals at particularly high risk of endometrial cancer who may benefit from targeted primary prevention strategies and to guide trial eligibility. On the basis of a systematic review of the literature, the evidence for inclusion of measures of obesity, reproduction, insulin resistance, and genetic risk in such a model is discussed, and the strength of association between these risk factors and endometrial cancer is used to guide the development of a pragmatic risk prediction scoring system that could be implemented in the general population. Provisional cutoff values are described pending refinement of the model and external validation in large prospective cohorts. Potential risk-reducing interventions are suggested, highlighting the need for future studies in this area if the increasing tide of endometrial cancer is to be stemmed. *Cancer Prev Res; 10(1); 1–13. ©2016 AACR.*

Introduction

Endometrial cancer is the fourth most common cancer in women in the United Kingdom, with more than 9,000 new diagnoses made in 2013 (1). The incidence is increasing not only in the developed world, where case numbers have more than doubled in the last 20 years but is also expected to increase in lower income countries as the global burden of obesity worsens (2). Given the current trajectory, it is predicted that by 2030, there will be an additional 3,700 new cases of endometrial cancer diagnosed each year in the United Kingdom (Fig. 1; refs.3, 4). In line with this, mortality rates are also increasing, albeit to a lesser extent, with a further 850 endometrial cancer deaths per year anticipated in England and Wales alone by 2030 (3). While endometrial cancer usually presents early, the morbidity associated with treatment, particularly in an increasingly elderly population, is not insignificant and disease recurrence, despite adjuvant treatment, continues to be a problem. Intervention is urgently required to stem this increasing tide of endometrial cancer if the effects, both for individual patients and for the health service, are not to become overwhelming.

Reducing the incidence of endometrial cancer requires the introduction of risk-reducing measures used selectively in those at greatest disease risk and targeted at key mechanisms driving endometrial carcinogenesis. Previously studied interventions have often been found to have only a modest effect on disease risk, mainly due to their application in relatively unselected populations with the result that more pronounced benefits for specific subgroups may be diluted (Table 1). This highlights the importance of developing better risk prediction models to identify specific patient groups in whom these candidate risk-reducing interventions can be trialed to maximize their potential impact.

Here, we propose a pragmatic risk prediction model to stratify the general female population into low-, medium-, and high-risk groups for endometrioid endometrial cancer, the most common histologic subtype (75% of all endometrial cancers; ref. 5) and for which there is the greatest understanding of underlying risk factors and potential carcinogenic mechanisms. Given that the number of cases peaks when women are in their mid to late 60s, such a model would be aimed at women aged 45–55 years with an intact uterus, allowing sufficient time for any benefit from prophylaxis to be realized. Experimental and epidemiologic evidence will be used to argue for the inclusion of measures of obesity (obesity score), unopposed estrogen exposure (reproductive risk score), insulin resistance (insulin resistance risk score), and family history (genetic risk score) to identify individuals at greatest risk and will include protective factors which may negate these risks. The rationale for using specific risk-reducing measures in subgroups based on their predominant endometrial cancer risk factor will also be explored.

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There are 2 limitations to this approach, which must be appreciated at the outset. While such a model is likely to have maximal impact on disease burden, it may not significantly reduce endometrial cancer mortality, as non-endometrioid tumors are more biologically aggressive and associated with poorer prognosis. The second point is that it may fail to protect women with undiagnosed Lynch syndrome in whom endometrial cancer often presents at an earlier age (<45 years); however, the model is designed to target the general population rather than those at a particularly high genetic risk of the disease (6).

Obesity Score

Any risk prediction model for endometrial cancer will be centered on measures of excess adiposity. It is estimated that up to 41% of endometrial cancer cases are directly attributable to women being overweight or obese and endometrial cancer has the strongest link with obesity of the 20 most common tumor types (6, 7). Several underlying mechanisms linking excess adiposity and endometrial cancer have been described; excess estrogen production, insulin resistance, and inflammation (Fig. 2). Each is discussed further in the relevant sections.

Numerous measures of obesity exist, but the most commonly used, cheapest and easiest to apply in a clinic setting is body mass index (BMI), calculated using the formula weight (kg)/height $(m)^2$.

BMI

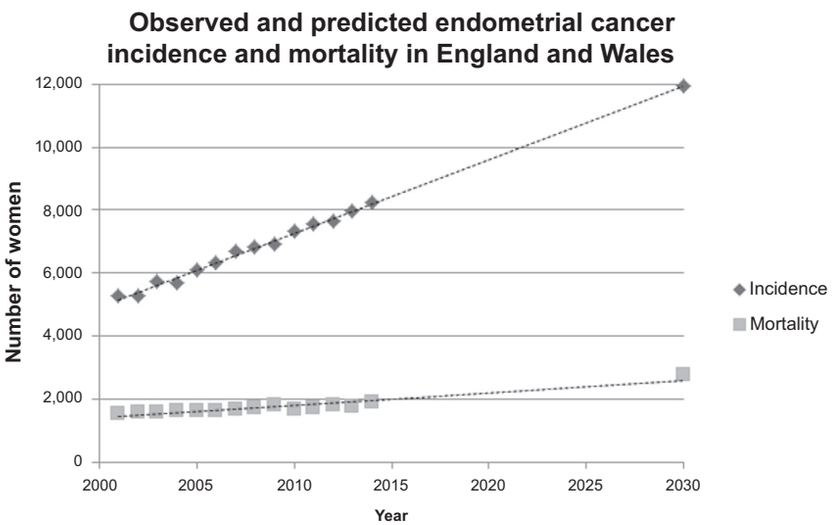
Meta-analyses of prospective observational studies have shown that a 5 kg/m^2 increase in BMI is associated with a 60% increase in the relative risk of developing endometrial cancer (6, 8). The effect is nonlinear although, with a proportionally greater increase in risk for each 5 kg/m^2 increase in BMI above 27 kg/m^2, such that a woman with a BMI of 42 kg/m^2 has a 9.11 times [95% confidence interval (CI), 7.26–11.51] greater risk of developing endometrial cancer than a woman with a BMI of 22 kg/m^2 (8). This is reflected in the final model, with additional weighting given to the presence of super obesity (Table 2).

Given this association, it would appear reasonable to offer weight loss surgery to reduce the risk of endometrial cancer in those at greatest risk of the disease (BMI $\geq$ 40 kg/m^2 along with additional risk factors for the disease). It is already known that there is a not insignificant prevalence of asymptomatic endometrial hyperplasia of 8.6% to 10% in the bariatric surgery population (women with BMI $\geq$ 40 kg/m^2 or BMI $\geq$ 35 kg/m^2 in the presence of obesity-related co-morbidities, such as diabetes mellitus or obstructive sleep apnea; refs.9–11). This risk is reduced by weight loss surgery; the prevalence of endometrial cancer has been shown to decrease from 1.4% to 0.4% in obese women following bariatric surgery (12). Even those persistently obese women, benefit from a 50% lowering of endometrial cancer risk following surgery, suggesting that metabolic changes, such as improvements in insulin sensitivity, are also important in this context (12). Additional health benefits associated with bariatric surgery include a reduction in the incidence of other obesity-related cancers, including postmenopausal breast and colorectal cancer, as well as resolution of diabetes, hypertension, angina, and obstructive sleep apnea (13). These benefits need to be incorporated into cost-effectiveness studies when determining the value of weight loss surgery in cancer prevention.

Focusing solely on women with the highest BMI ($\geq$40 kg/m^2), however, limits the benefits from endometrial cancer prevention to only 3% of the female population (14). Other measures of adiposity, such as central obesity and weight gain over time, can also be used to identify those women with lower BMIs who also have a particularly high risk of developing endometrial cancer.

Body Fat Distribution

Body fat distribution is potentially a better predictor of cancer risk for obesity-associated malignancies than BMI, especially in breast cancer (15). Measures which assess the extent of central versus peripheral obesity can, therefore, be useful to further



Data obtained from the Office for National Statistics and Welsh Cancer Intelligence and Surveillance Unit.

····· Predicted number of cases based upon current trajectory

Figure 1.
Observed and predicted endometrial cancer incidence and mortality data from England and Wales. Given the current trajectory of increasing endometrial cancer incidence and mortality, by 2030, it is estimated that there will be an additional 3,700 new cases diagnosed each year in England and Wales and 850 further deaths from the disease.

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Table 1. Candidate prophylactic interventions trialed in endometrial cancer prevention and their relative merits

Intervention	Target population	Mechanism of action	Current evidence	Side effects	Contraindications	Potential problems
Low-fat diet (≤20% of energy from fat)	BMI > 30 kg/m^2	• Decrease adiposity and weight • Decrease serum estrone, estradiol, and testosterone levels (67) • Increase sex hormone–binding globulin levels (67) • Improved insulin sensitivity (68)	• Low-fat diets *per se* do not prevent endometrial cancer if they are not associated with significant weight loss (69) • Self-reported prior weight loss of 20 lbs or more in a single episode associated with a nonsignificant 7% reduction in risk of endometrial cancer (70) • Lower insulin and HOMA-IR levels found after 3 mo of an intermittent fasting diet, where only 600–650 cal/d are consumed on 2 d/wk, compared with a continuous low-calorie diet. No difference in amount of weight loss between groups but reduction in fat mass and improved compliance in intermittent fasting group (68). No studies of the effect of intermittent fasting on cancer prevention in humans have yet been published.	Nil	Nil	• Long-term compliance often low with weight gain noted after discontinuing intervention. • Excessive rebound weight gain may exacerbate endometrial cancer risk
Physical activity	BMI ≥ 25 kg/m^2	• Decrease adiposity and weight • Improve insulin sensitivity and reduce insulin levels (71) • Reduce serum estradiol and increase sex hormone–binding globulin levels (71) • May improve innate and acquired immune responses (71)	• One hour daily of moderate intensity activity likely to reduce endometrial cancer risk, with the most active women benefitting from a 20%–30% risk reduction, independent of adiposity (72). Higher intensity, longer duration exercise likely to be best, though all activity types lower endometrial cancer risk by a similar amount. Benefit restricted to overweight/obese women (73). • No clinical trials undertaken looking at increasing physical activity as a primary prophylactic intervention against endometrial cancer	Nil	Other co-morbidities limiting exercise capacity	• No consensus reached on from what age physical activity is beneficial or for how long it needs to be maintained. • Compliance likely to be lower if long-term intervention required.

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Table 1. Candidate prophylactic interventions trialed in endometrial cancer prevention and their relative merits (Cont'd)

Intervention	Target population	Mechanism of action	Current evidence	Side effects	Contraindications	Potential problems
Bariatric surgery	BMI $\geq$ 40 kg/m^2 or $\geq$35 kg/m^2 in the presence of obesity-related co-morbidities, e.g., diabetes, obstructive sleep apoea	• Decrease adiposity and weight (either through calorie restriction, malabsorption, or decrease in appetite) • Improvement in insulin sensitivity (74) • Decrease in oxidative stress and inflammation (75) • Lowering leptin levels and increase in adiponectin (74) • Decrease sex steroid levels and normalize endometrial hormone receptor expression (76)	• Bariatric surgery associated with a 70%–80% reduction in endometrial cancer risk compared with obese control women, with a greater benefit seen for women achieving normal body weight following the procedure (12, 77). • Benefit still remains, albeit smaller, for those who fail to lose weight after the procedure (12)	• Surgical complications, including anastomotic leak • Malabsorption (depending upon type of surgical procedure) • Risk of perioperative mortality	• Patient not motivated to undergo procedure • Medically unfit to undergo surgical procedure • Alcohol or substance misuse • Uncontrolled psychiatric problems	• Estimated that 71 bariatric procedures would need to be conducted to prevent 1 incident endometrial cancer, although patients would also benefit from resolution of diabetes and improvements in cardiovascular disease (77) • May only be cost-effective for those at greatest endometrial cancer risk • Requires patient to be motivated to adapt dietary pattern
Metformin	• Insulin resistant-HOMA-IR >2.8 • PCOS	• Improve insulin sensitivity and lower insulin levels • Reduction in estrogen-stimulated expression of proto-oncogenes c-fos and c-myc in animal studies (78) • Increase in endometrial progesterone receptor expression (79) • Inhibition of TNFα signaling, at least in vascular endothelial cells (80)	• Limited evidence of benefit from small numbers of women with endometrial hyperplasia desiring fertility preservation. Treatment with metformin associated with resolution of atypia and reduction in insulin, glucose, and testosterone levels (81–83). • Difficult to determine whether benefit solely due to metformin although as some women co-treated with COCP (82)	Gastrointestinal upset- nausea/ vomiting, diarrhea Rash	Severe renal disease Severe liver disease Alcohol abuse	• Identifying insulin-resistant population difficult due to lack of standardization of testing • No benefit in terms of endometrial cancer risk reduction seen for diabetic patients taking metformin with the aim of lowering serum glucose (84)
COCP	• PCOS • Oligomenorrhea • Lynch syndrome	• Reduction in endometrial proliferation	• Ever use of COCP associated with a 40%–50% reduction in endometrial cancer risk, with benefit continuing even after discontinuation of use (29, 85) • Only clinical trial of COCP for the prevention of endometrial cancer carried out in women with Lynch syndrome; 3-month use associated with a significant reduction in endometrial proliferation, IGF-1 and -2 levels and increase in IGFBP-1 levels. Long-term benefit in terms of reducing endometrial cancer risk not assessed (86) • Additional benefit of reducing ovarian cancer risk by 20% for each 5 years of use (87)	Headache, breast tenderness, breakthrough bleeding, increased risk of venous thromboembolism, increased risk of breast and cervical cancers (risk returns to normal once use discontinued)	Pre-existing cardiovascular disease, family history of thrombosis, morbid obesity, smoker age >35 y	Decision analytical model suggested that 5 y of COCP use in obese women was unlikely to be a cost-effective strategy for decreasing endometrial cancer incidence, although failed to take into account the reduction in ovarian cancer risk. Selection of subgroups on the basis of longstanding anovulation or morbid obesity may improve cost-effectiveness (88)

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Table 1. Candidate prophylactic interventions trialed in endometrial cancer prevention and their relative merits (Cont'd)

Intervention	Target population	Mechanism of action	Current evidence	Side effects	Contraindications	Potential problems
Levonorgestrel-releasing intrauterine system (Mirena)	• Tamoxifen users • Estrogen-only HRT users • Obese women	• Downregulation of endometrial estrogen receptors and reduction in cellular proliferation (89)	• Use of levonorgestrel-releasing intrauterine system for the treatment of heavy menstrual bleeding associated with a 54% reduction in endometrial cancer compared with premenopausal controls and up to 75% reduction with prolonged use (32). Follow-up limited to age 55, so may have underestimated benefit by excluding age group with highest endometrial cancer incidence. • Use associated with protection against endometrial hyperplasia in tamoxifen and estrogen-only HRT users (90) • Current ongoing study by our own group investigating the role of the levonorgestrel-releasing intrauterine system in the primary prevention of endometrial cancer in obese women	Irregular bleeding (usually settles within 6 mo), coil expulsion, failed insertion, uterine perforation during insertion, endometritis, breast tenderness, mood swings	Breast cancer, unexplained vaginal bleeding, cervical cancer, liver disease, stroke, untreated pelvic infection	Benefit in asymptomatic, obese population yet to be determined
Aspirin	BMI $\geq$ 30 kg/m^2	• Anti-inflammatory effect • Reduction in aromatase and estrogen levels (61) • Increased apoptosis (62)	• Meta-analysis of observational studies found a small, nonsignificant reduction in endometrial cancer risk with long-term aspirin in the general population (91). • Obese women may derive greater benefit, although. • Similar results seen for women with Lynch syndrome taking aspirin for 4 years for the primary prevention of endometrial cancer (64). In colorectal cancer cell lines, nitric oxide donating aspirin suppressed microsatellite instability in MMR-deficient cells and is thought to lower the threshold for apoptosis in response to DNA damage (92)	Indigestion, gastrointestinal bleeding, peptic ulcer	Bleeding disorders, allergy to nonsteroidal anti-inflammatories, renal disease, caution in asthma	Minimal benefit seen in general population, further studies required to determine whether particular subgroups likely to derive greater benefit from aspirin prophylaxis

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Table 1. Candidate prophylactic interventions trialed in endometrial cancer prevention and their relative merits (Cont'd.)

Intervention	Target population	Mechanism of action	Current evidence	Side effects	Contraindications	Potential problems
Vitamin D	BMI $\geq$ 30 kg/m^2	• Inhibition of cell proliferation • Reduction in angiogenesis (93)	• No association between vitamin D levels and total dietary vitamin D intake and endometrial cancer risk (94). • Evidence of a benefit from vitamin D supplementation limited to animal studies using obese Pten (+/−) mice (95)	None with doses up to 10,00 IU/d high doses-bone demineralization, hypercalcemia	Primary hyperparathyroidism, hypercalcemia, caution if taking digoxin	• No evidence of benefit in general population. • Further studies required to determine whether vitamin D supplementation effective in obese women particularly in reducing endometrial cancer risk
Coffee consumption ($\geq$4 cups of coffee/d)	Non/low coffee consumers	• Increase sex hormone–binding globulin levels (96) • Improve insulin sensitivity (97) • Inhibit oxidative damage, anti-inflammatory effect • Induction of cellular defenses and DNA repair • Detoxification of potential carcinogens (98)	• Increased coffee consumption associated with lower endometrial cancer risk. • Seven percent reduction in endometrial cancer risk with each one additional cup of caffeinated coffee drunk per day and 4% reduction with decaffeinated coffee (99). Benefit restricted to women with BMI >25 kg/m^2 and those who have never used hormone therapy. • No studies investigating coffee drinking specifically for endometrial cancer prophylaxis	Insomnia, restlessness, tachycardia, headache, nausea/vomiting (related to caffeine)	Cardiac problems, particularly arrhythmias	• Potential confounding of results from case–control studies cannot be excluded • Side effects likely to limit number of cups of coffee that can be consumed each day

stratify patients within a particular BMI category. This can easily be performed using a ratio of waist to hip circumference; a value greater than 0.8 is consistent with central adiposity and an adverse metabolic phenotype, even in individuals with a normal body weight (16).

Despite the findings in other cancer types, the endometrial cancer literature is divided as to whether there is an independent relationship between waist:hip ratio and endometrial cancer risk (17–19). Importantly, studies with the most discrepant results were undertaken in markedly dissimilar populations, with significantly different proportions of obese women. After adjusting for BMI, a meta-analysis of prospective observational studies found a nonsignificant increase in endometrial cancer risk with each 0.1-unit increase in waist:hip ratio [relative risk (RR), 1.07; 95% CI, 0.97–1.17; ref. 19]. Individually, however, both waist and hip circumference were independently associated with disease risk (RR, 2.16 and 1.30 per 10-cm increase in waist and hip circumference, respectively). These studies, however, were noted to be heterogeneous in design and frequently relied on self-reported measurements, which can be particularly difficult to perform in obese women where waist and hip landmarks are more problematic to identify (17).

Effect of Weight Change

While current BMI has a significant influence on endometrial cancer risk, weight change over time is also important and is factored into the risk prediction model. This is based on results from the meta-analysis discussed above, in which an increase in weight between the ages of 18 and 20 years and middle age was associated with a higher endometrial cancer risk, even after adjusting for current BMI (19). For each 5-kg increase in weight over this time period, the risk of endometrial cancer increased by 18% (95% CI, 15%–21%). Importantly, this result has been replicated in a non-Western population, with lower overall levels of obesity, and may be more pronounced in women with a higher starting BMI in their late teens/early twenties (20). The caveat to the use of weight gain in a predictive model of endometrial cancer risk is its reliance on estimates of historical weight and the inaccuracies inherent to such data.

Adipokines

In addition to clinical measurements of body mass and adiposity distribution, adiponectin levels are also included as a serum biomarker of obesity and an adverse metabolic phenotype. Adiponectin is secreted by adipose tissue, although levels are inversely correlated with BMI (21). Biologically, it has an anticancer effect, acting as an anti-inflammatory and improving insulin sensitivity, while inhibiting angiogenesis and downregulating vascular adhesion molecule expression (22). This is achieved through activation of AMPK and inactivation of ERK and MAPK (Fig. 2). It is also able to increase apoptosis by inducing expression of p53 and Bax, thereby acting as a negative regulator of tumor formation (23). Higher serum levels of adiponectin are associated with a reduction in endometrial cancer risk (summary: OR, 0.47; 95% CI, 0.34–0.65) with evidence of a dose–response relationship (24). For each 5 μg/mL increase in adiponectin levels, the risk of endometrial cancer has been found to decrease by 18%, an effect consistent across analyses adjusted for confounding factors, such as menopausal status, BMI, and hormone replacement therapy (HRT) use. This supports the distinction between

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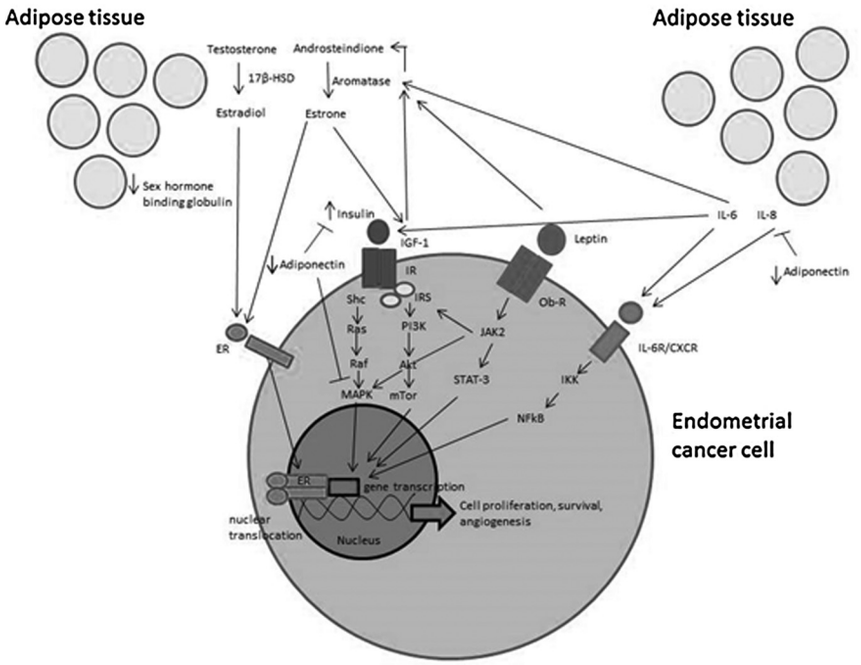

Figure 2.
Summary of pathways linking obesity with endometrial cancer development. Obesity contributes to endometrial carcinogenesis through 3 separate, but closely interconnected, mechanisms; aromatization of androgens into proproliferative estrogens, an increase in local production of the mitogens insulin and IGF-1 through a reduction in insulin sensitivity, and the chronic release of high levels of inflammatory mediators.

Abbreviations: 17β-hydroxysteroid dehydrogenase (17β-HSD), interleukin-6 (IL-6), IL-6 receptor (IL-6R), chemokine receptor (CXCR), leptin receptor (Ob-R), Janus Kinase 2 (JAK2), signal transducer and activator of transcription 3 (STAT-3), IkB kinase (IKK), insulin receptor (IR), oestrogen receptor (ER)

metabolically healthy and metabolically unhealthy obese individuals and is incorporated into the risk prediction model as a protective factor (25).

At present, there is insufficient evidence to support the inclusion of the other important adipokine, leptin, in the risk model. It is also secreted by adipocytes and is involved in energy homeostasis, with levels increasing in proportion with body mass (26). It has multiple cellular effects *in vitro*, any or all of which are associated with an increased risk of tumor formation, including proinflammatory, proangiogenic, mitogenic, and antiapoptotic effects, through activation of *MAPK, PI3K,* and *STAT* pathways and increases in aromatase activity (26). While a meta-analysis of observational studies found that women with leptin levels in the upper tertile had a 2-fold increase in their risk of endometrial cancer compared with those with the lowest levels, independent of BMI, the included studies were heterogeneous in design and inclusion criteria and insufficient data were available to determine whether a dose–response relationship existed. Further work is, therefore, required to quantify the relationship between leptin levels and endometrial cancer risk before it can be included in any prediction model.

Each of the obesity measures discussed is derived from good quality epidemiologic and *in vitro* evidence demonstrating a dose–response relationship between excess adiposity and endometrial cancer risk. While they are included to measure different aspects of this association, to avoid "double counting" obesity in the risk prediction model, the highest score of any of the clinical obesity measures added to the serum adiponectin score will be combined with the reproductive, insulin, and genetic risk scores to derive the overall score.

Reproductive Risk Score

Established reproductive risk factors for endometrial cancer can be interpreted in light of the "unopposed estrogen theory". Estrogen induces endometrial proliferation through local production of IGF-1, increasing the risk of accumulation of genetic mutations in proto-oncogenes and tumor suppressor genes (27). It is also responsible for an increase in free radical–mediated DNA damage and inhibition of apoptosis (26, 27). Increased lifetime exposure to estrogen, through early menarche (<12 years) or late menopause (≥55 years) is, not surprisingly, associated with an increased risk of endometrial cancer (28). While estrogen only HRT is a time-honored risk factor for endometrial cancer, it is now so rarely used in women with an intact uterus that it has not been included in the risk prediction model. Conversely, use of the combined oral contraceptive pill (COCP) for ≥5 years is associated with a significant reduction in endometrial cancer risk due to suppression of endogenous estrogen levels and increased exposure to progesterone throughout the menstrual cycle (29). For the same reason, increasing parity is a protective factor; a meta-analysis of 46 studies showed that, compared with nulliparous women, women who had had one child had a 27% lower risk of developing endometrial cancer (RR, 0.73; 5% CI, 0.64–0.84) and those with 2 children a 38% reduction in endometrial cancer risk (RR, 0.62; 95% CI, 0.53–0.74; ref. 30). While there was some evidence of a dose–response relationship between parity and endometrial cancer risk, the numbers of included women with 3 or more children were too small to draw meaningful conclusions from.

For postmenopausal women, adipose tissue becomes the dominant source of estrogen, responsible for the conversion of

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Table 2. Proposed endometrial cancer risk prediction model

Risk score	Risk factor	−2	−1	0	1	2	4	8
	BMI			<25 kg/m^2	25–30 kg/m^2	30–35 kg/m^2	35–40 kg/m^2	≥40 kg/m^2
	Waist circumference			<90 cm	90–100 cm	100–110 cm	>110 cm	
Obesity	Weight gain between 18–25 and 45–55 y			<5 kg	5–20 kg	>20 kg		
	Adiponectin	>5 μg/mL		<5 μg/mL				
Reproductive	Early menarche (<12 y) or late menopause (>55 y) OR Anovulation (6 mo of more, unrelated to pregnancy, breastfeeding, or contraceptive use)			None	One or more			
	Parity	2+	1	0				
	COCP use	≥5 y		Never or <5 y				
	Ever use of tamoxifen			No		Yes		
	Free testosterone			≤17 pmol/L	>17 pmol/L			
Insulin	Type 2 diabetes			Absent		Present		
	PCOS			Absent			Present	
	C-peptide (non-fasting)			≤0.76 nmol/L		>0.76 nmol/l		
Genetic	Family history of endometrial cancer			No first- or second-degree relatives affected			First-degree relative diagnosed at <50 years of age	Two or more first- or second-degree relatives diagnosed

NOTE: Points are assigned as described for each individual risk factor. The highest single clinical obesity score is then added to the serum adiponectin score to give the final obesity score. This is combined with the total reproductive, insulin, and genetic scores to give an overall total, which is used to assign patients into risk categories: 0–2 low risk, 3–7 medium risk, ≥8 high risk.

androstenedione and testosterone into estrogen and estradiol by aromatase and 17β-hydroxysteroid dehydrogenase (17β-HSD) produced by adipocytes (28, 31). Obesity hence plays a significant role in postmenopausal estrogen production and also increases its bioavailability by reducing sex hormone–binding globulin production (Fig. 2).

Increased estrogen levels are not seen in premenopausal women who develop endometrial cancer; however, instead a relative deficiency of progesterone appears to be important. Progesterone counteracts the mitogenic effects of estrogen by increasing synthesis of IGF = binding protein-1 (IGFPB-1) to mop up excess IGF-1 and promoting expression of the estrogen sulfotransferase and 17β-HSD enzymes, to convert estradiol into the less potent estrone (27). Women with prolonged periods of anovulation, such as those with polycystic ovary syndrome (PCOS), are not exposed to the protective effects of progesterone during the luteal phase of the menstrual cycle and are at heightened risk of endometrial cancer. In contrast, users of progesterone—releasing intrauterine systems (Mirena)—have a significantly lower risk of endometrial cancer than non-users (standardized incidence ratio, 0.46; 95% CI, 0.33–0.64; ref. 32).

Tamoxifen, a selective estrogen receptor modulator, is used to treat and less frequently prevent breast cancer, by inhibiting the growth of breast cancer cells. This is at the expense, however, of stimulating endometrial proliferation, resulting in a 2- to 3-fold increase in the risk of developing endometrial cancer for tamoxifen users (33, 34). This effect appears to be restricted to postmenopausal women exposed to the drug. The risk of endometrial cancer increases with duration of exposure and dose used, although even low doses used for 2 years are associated with an increased risk of disease (35, 36). This effect appears to persist even after its discontinuation. Ever use of tamoxifen, therefore, is included as a risk factor in the prediction model.

Previous risk prediction models incorporating these reproductive risk factors have produced varying results depending upon the population studied. When performed using the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort of both pre- and postmenopausal women, inclusion of these variables improved the discriminatory capability of the model over the use of age alone in predicting endometrial cancer, with an overall *C*-statistic of 77% (37). In contrast, Pfeiffer and colleagues (38) found a significant overprediction of endometrial cancer risk in their postmenopausal population using a similar model. The ability of our prediction model to accurately identify those at increased risk of endometrial cancer is enhanced through the inclusion of serum biomarkers of reproductive risk alongside these epidemiologic risk factors (Table 2).

The decision to include androgen levels was based on data from large prospective nested case–control studies, which have shown that levels of total and, especially, free testosterone are increased in endometrial cancer cases compared with healthy controls (39). While there is insufficient data available in the literature to determine optimal cutoff values, free testosterone levels of >17 pmol/L appear to be associated with the development of endometrial cancer in both pre- and postmenopausal women (39, 40). This effect is independent of BMI and precedes a diagnosis of

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endometrial cancer (by a median of 11.2 years), allowing adequate time for prophylactic intervention to be instituted. Measurement of serum-free androgens also has the advantage that levels are unaffected by the menstrual cycle, avoiding the complexities of timing blood sampling that is seen with other sex hormones. It is as yet unclear whether elevated androgen levels are associated with an increased risk of developing premenopausal endometrial cancer as the study by Clendenen and colleagues (40) found no association if a diagnosis was made prior to the age of 55 years, although their analysis was based on only 49 cases and 86 controls. The molecular effect of testosterone on the endometrium and endometrial cancer cells is still debated, but it would appear logical for it to be included in the prediction model, given the close association between elevated androgen levels, obesity, and estrogen production in postmenopausal women and PCOS in younger individuals (40).

Measurement of serum estrogen levels was discounted from the model on the basis that it was only of value in determining endometrial cancer risk in postmenopausal women. Several case–control and prospective cohort studies have found increased levels of endogenous total and free estrogen in postmenopausal women with endometrial cancer compared with controls, with estradiol levels in the upper tertile being associated with a 2- to 4-fold increase in endometrial cancer risk (27, 41, 42). In premenopausal women, however, this relationship is not evident, limiting its applicability in our target population (43). There are no published studies evaluating progesterone as a marker of endometrial cancer risk, although as levels vary dramatically throughout the menstrual cycle, attempting to control for this would be difficult (27).

Insulin Risk Score

The third component of the risk prediction model, and an area receiving increasing attention, is the effect of insulin resistance on the development of endometrial cancer. There is now substantial *in vitro* evidence for a direct effect of insulin and IGF-1 on endometrial cancer cells, with activation of the insulin receptor resulting in an increase in cell proliferation and inhibition of apoptosis (44, 45). These effects are mediated through both the MAPK and PI3K/Akt pathways (Fig. 2). Insulin and IGF-1 also stimulate β-catenin, a signaling pathway involved in early tumor formation, and through this the oncogene Ras. By increasing the breakdown of IGFBP-3, insulin is able to act to increase levels of free IGF-1 and thus enhance its tumor-promoting capacity. Beyond these direct effects, hyperinsulinemia is also involved in increasing ovarian androgen production and peripheral aromatization to estrogen, reducing sex hormone–binding globulin and adiponectin levels and stimulating leptin secretion, highlighting the interdependence of these mechanisms (44).

In line with this, a diagnosis of type 2 diabetes mellitus is included in the model as its presence is associated with a greater than 2-fold elevation in endometrial cancer risk, even after adjustment for activity levels and BMI (46). Similarly, PCOS, while featuring in the reproductive risk score because of its link with hyperandrogenemia, is also included in the insulin risk score; 50% to 70% of patients with PCOS are also insulin-resistant and this group has a particularly high endometrial cancer risk (47). Despite the epidemiologic evidence supporting an increased risk of endometrial cancer for those with elevated insulin levels, large-scale testing is not possible due to the lack of a standardized protocol for sample preparation and testing and the absence of validated cutoff values to stratify patients into high- and low-risk groups (48–51). For these reasons, surrogate measures of insulin sensitivity, such as HOMA-IR and QUICKI, which rely on accurate insulin level measurements, have also not been included. The gold-standard test of insulin sensitivity is the euglycemic clamp test, but this is too expensive and time-consuming to be used apart from on an individual patient basis (52). While measurement of IGF-1 levels would circumvent many of these problems, no consistent association between serum IGF-1 and endometrial cancer risk has been demonstrated, suggesting that local endometrial IGF-1 production may be more relevant than systemic levels (51).

On the basis of current evidence and with mind to the practicalities of screening a large number of patients, we propose incorporating the pro-insulin protein, C-peptide, into a risk prediction model. It is stored intracellularly with insulin and the 2 are released together in equal amounts; higher levels of C-peptide thus reflect increased endogenous insulin secretion and insulin resistance. It has the advantage of having a longer half-life than insulin and more accurately reflects insulin levels if there is variation in fasting time. An absolute requirement for fasting samples is also not necessary. Five observational studies have been conducted examining the relationship between C-peptide levels and endometrial cancer, the results of which were combined in a meta-analysis (49). Both fasting and non-fasting levels were significantly higher in patients who subsequently developed endometrial cancer than in controls, with evidence of a dose–response relationship (51, 53). Only one study reported on actual C-peptide levels rather than study-specific quintiles; a level greater than 0.76 nmol/L is associated with 1.5- to 2-fold elevation in endometrial cancer risk and is used in the model (53).

Glycosylated hemoglobin (HbA1C) is now part of both the World Health Organization (WHO) and National Institute for Health and Care Excellence (NICE) recommendations for diagnosing type 2 diabetes and validated clinical laboratory protocols are already in place for its measurement. It represents glycemic control over a preceding 8- to 12-week period and can be measured at any time of day without the requirement for fasting, making it easier to measure than fasting glucose levels or performing an oral glucose tolerance test (OGTT). There is, however, insufficient evidence to support its inclusion in the risk prediction model, at present. Only one study has been performed examining the relationship between HbA1C levels and endometrial cancer risk and was insufficiently powered to determine cutoff values for inclusion here (54). It did suggest, although, that even modest elevations in HbA1C in nondiabetic patients may significantly increase cancer risk. Further work is clearly warranted in this area.

Genetic Risk Score

The risk of endometrial cancer in women with Lynch syndrome (mutations in the DNA mismatch repair genes MSH2, MSH6, MLH1, PMS2, or EPCAM) is significantly elevated, with a cumulative risk of endometrial cancer of 16% to 71% by the age of 70 years, depending upon the specific gene affected (55, 56). Despite this, the role of screening for endometrial cancer in women with Lynch syndrome and the value of prophylactic intervention to reduce this risk have yet to be clearly defined and is the subject of ongoing research. As this model has been developed for use in the general population, this topic will not be discussed further here.

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Irrespective of the underlying genetic predisposition, a family history of endometrial cancer is associated with a significant increase in endometrial cancer risk, particularly if a first-degree relative was diagnosed before the age of 50 years (HR, 6.68; 95% CI, 4.02–11.1; $P < 0.001$; ref. 57). This risk is increased further if 2 or more first- or second-degree relatives have previously had endometrial cancer (HR, 8.73; 95% CI, 4.25–17.9; $P < 0.001$). The risk of endometrial cancer for women with a family history of colorectal cancer is much lower and overall not significantly higher than for women without a family history. While both inherited mutations in genes critical to endometrial carcinogenesis and the presence of shared risk factors (including obesity) for the condition may explain this association, the exact mechanisms have yet to be determined.

Inflammation

While not directly incorporated at present, future work may well see measures of inflammation feature in the risk prediction model. Adipose tissue is increasingly being recognized as playing an active role in many diseases, including cancer, through the release of adipokines, cytokines, and sex hormone metabolism (58). Obesity is, itself, a state characterized by chronic inflammation (59). Cytokines are produced by activated adipocytes and infiltrating macrophages in response to adipose tissue expansion and localized hypoxia. Increasing BMI and waist circumference are associated with elevated levels of cytokines including IFNs, IL6, IL8, IL1 receptor antagonist (IL-1Ra), and C-reactive peptide (CRP; refs.26, 60, 61).

Endometrial carcinogenesis may be promoted by this inflammatory milieu. Chronic inflammation results in the generation of free radicals, increased concentrations of COX2 and prostaglandin E2, and leads to cell proliferation and DNA damage (62). Activation of the NF-κB pathway by inflammatory cytokines is responsible for inhibition of apoptosis, overcoming cell-cycle arrest and the transcription of genes encoding proinflammatory cytokines, thereby establishing a vicious cycle of inflammation, resulting in tumor formation (Fig. 2). Inflammation also contributes to the development of insulin resistance and IL6 stimulates aromatase activity and the conversion of androgens into estrogen within adipose tissue (61). Nested case–control studies within the EPIC and Women's Health Initiative cohorts found higher levels of inflammatory mediators to precede a diagnosis of endometrial cancer, although the association was largely dependent on the degree of adiposity (61, 63). There is, however, some debate about which cytokines are specifically elevated in endometrial cancer and the optimal laboratory technique for their measurement. In particular, these proteins may be too nonspecific to be used in a risk prediction model; levels are elevated transiently in numerous situations, including subclinical infection. Longitudinal, prospective cohort studies are required to evaluate the role of inflammatory cytokines, such as IL6 and CRP, in endometrial cancer risk stratification and to determine whether repeated measures over time are of greater predictive value than one-off measurements. Should this evidence be forthcoming, it would support the targeted use of aspirin as a prophylactic intervention for those with an increased inflammation risk score. This has already been shown to be the case for women with Lynch syndrome in the CAPP2 study, where treatment with aspirin for $\geq$2 years was associated with a 53% reduction in the incidence of endometrial cancer, although the mechanism underpinning this effect may well be different (64).

Using the Risk Prediction Model to Target Prophylaxis

The 4 individual components of the risk prediction model, genetic (G), insulin (I), reproductive (R), and obesity (O) scores, are combined to give an overall assessment of endometrial cancer risk, stratified into low-, medium-, and-high risk groups (Table 2, Fig. 3). On the basis of an absolute lifetime risk of the disease of 2.4%, this approximates to an absolute risk of endometrial cancer of up to 4.9%, 7.3% to 17.1%, and $\geq$19.5% for the low-, medium-, and high-risk groups, respectively (65). The

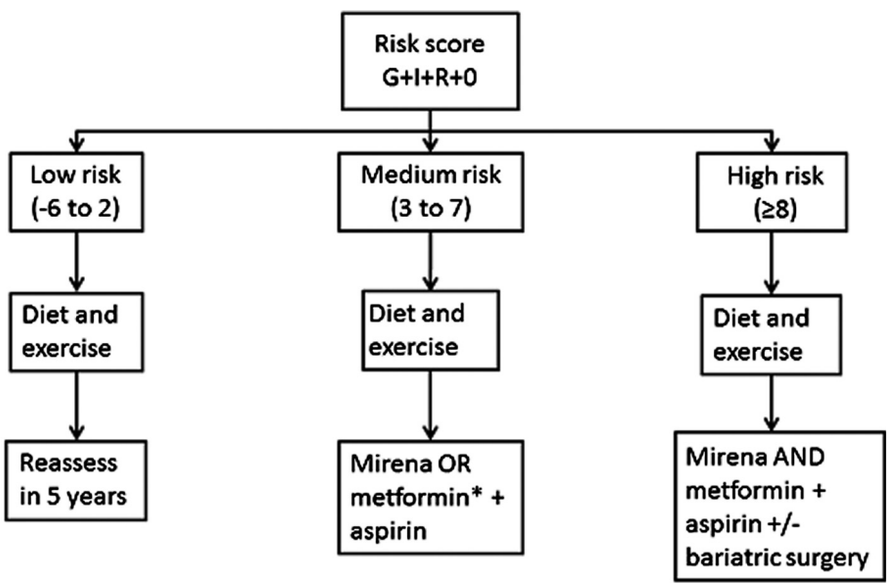

Figure 3.
Proposed triage of women using the risk prediction model to prevention strategies. Genetic, insulin, reproductive, and obesity scores are combined and used to triage patients into low-, medium-, and high-risk groups. Women in the low-risk category are offered diet and exercise advice and their risk score repeated in 5 years, while those in the medium-risk group are offered prophylactic intervention in the form of aspirin and a Mirena coil or metformin, depending upon whether the reproductive risk or insulin risk score is higher, respectively. Women in the highest risk group are offered aspirin, Mirena and metformin prophylaxis and are referred for bariatric surgery, if appropriate.

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predominant risk factor identified can be used to determine the type of prophylactic intervention trialed, for example, metformin when the insulin score is particularly high, the COCP or levonorgestrel-releasing intrauterine device if the reproductive score predominates.

The "optimal" model for risk prediction will include all the clinical and serum biomarkers incorporated into Table 2, to identify undiagnosed risk factors, particularly the presence of insulin resistance, within an asymptomatic population. Where blood draw is not possible, a model based on the clinical risk factors alone can be employed, although this is likely to underestimate disease risk in some women. For those deemed low risk, diet and exercise advice alone is required; this can be as simple as encouragement to maintain a normal BMI for those with a negative risk score to more intensive dietetic input and exercise advice for those with a BMI > 25 kg/m^2. Lifestyle education such as this is vital not only to limit endometrial cancer risk but also to prevent an increase in risk of other malignancies and cardiovascular disease. Whether women given an individualized risk assessment are more likely to heed advice about lifestyle modification to induce weight loss is currently unknown; the concept of a "teachable moment" to positively influence behavior is a hotly debated topic.

Women within the medium = risk group could receive the diet and exercise advice along with aspirin and metformin or a levonorgestrel-releasing intrauterine system (Mirena, Table 1), depending upon whether their highest score is in the reproductive or insulin risk categories. For those patients already taking metformin, a review of the dose and compliance with treatment is warranted, with the addition of further hypoglycemic medication indicated if glycemic control cannot be optimized further.

Those within the high-risk category require multimodal intervention to reduce their endometrial cancer risk, including diet and exercise advice, aspirin, metformin, and a Mirena coil. For women with a BMI $\geq$ 40 and other endometrial cancer risk factors (particularly diabetes), bariatric surgery should also be offered; such a procedure would not only provide endometrial protection but also be associated with significant reductions in weight and improvements in insulin resistance.

Reassessment of endometrial cancer risk using the prediction model is likely to be required every 5 years. This allows the Mirena coil to be replaced, if necessary, to ensure continuing efficacy and change or introduce other prophylactic treatments depending upon an individual's risk score. Such assessments will continue until age 70, at which point the number of cases of the disease naturally declines and evidence for the validity of the components of the risk prediction model and prophylactic treatments discussed becomes more circumspect.

Conclusion

Mechanistic and epidemiologic studies have provided useful information on which to guide the development of a prediction model for endometrial cancer risk. We propose that such a model should include measures of obesity, reproductive hormones, insulin resistance, and family history, reflecting the interconnection of these mechanisms in driving endometrial cancer development. As it stands, this model is purely theoretical and requires formal testing in a large prospective cohort of asymptomatic women for whom long-term outcome data are available. This will allow the model to be refined, using random decision forests and unconditional logistic regression, to optimize the weighting of included variables and ensure its accuracy in identifying individuals at high and low risk of the disease. Once calibrated, we propose to validate the model in a second, independent cohort, thereby verifying its applicability to the general population. The UK Biobank, with its recruitment of more than 250,000 women and inclusion of anthropometric, biochemical, and clinical follow-up data, will provide the ideal resource in which to conduct this work (66). With periodic release of information, the Biobank is a not-for-profit organization established to assist researchers in understanding disease-specific risk factors and the development of such prediction models. This information would not only allow the identification of individuals with a particularly high risk of developing endometrial cancer but also potentially guide the development of prophylactic treatment aimed at specific disease-causing targets, such as insulin resistance and inflammation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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References

1. Cancer Research UK. Uterine (womb) cancer incidence statistics. Cancer Stats: Cancer Statistics for the UK; 2014[cited 2014 Oct 17]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/incidence.
2. Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol 2015;16:36–46.
3. Office for National Statistics. Cancer Registration Statistics, England; 2016[cited 2016 May 18]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland.
4. Welsh Cancer Intelligence and Surveillance Unit. Cancer statistics data tables; 2016[cited 2016 May 18]. Available from: http://www.wcisu.wales.nhs.uk/officical-statistics-exel-files-of-trend
5. Murali R, Soslow RA, Weigelt B. Classification of endometrial carcinoma: more than two types. Lancet Oncol 2014;15:e268–78.
6. 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.
7. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet 2014;384:755–65.
8. Crosbie EJ, Zwahlen M, Kitchener HC, Egger M, Renehan AG. Body mass index, hormone replacement therapy, and endometrial cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2010;19:3119–30.
9. Argenta PA, Kassing M, Truskinovsky AM, Svendsen CA. Bariatric surgery and endometrial pathology in asymptomatic morbidly obese women: a prospective, pilot study. BJOG 2013;120:795–800.

Published OnlineFirst December 13, 2016; DOI: 10.1158/1940-6207.CAPR-16-0224

10. Modesitt SC, Hallowell PT, Slack-Davis JK, Michalek RD, Atkins KA, Kelley SL, et al. Women at extreme risk for obesity-related carcinogenesis: Baseline endometrial pathology and impact of bariatric surgery on weight, metabolic profiles and quality of life. Gynecol Oncol 2015;138:238–45.
11. Mackintosh M. The impact of obesity and weight loss on the malignant potential of endometrium. 2016.
12. Ward KK, Roncancio AM, Shah NR, Davis MA, Saenz CC, McHale MT, et al. Bariatric surgery decreases the risk of uterine malignancy. Gynecol Oncol 2014;133:63–6.
13. Douglas IJ, Bhaskaran K, Batterham RL, Smeeth L. bariatric surgery in the United Kingdom: A cohort study of weight loss and clinical outcomes in routine clinical care. PLoS Med 2015;12:e1001925.
14. Public Health England. Obesity; 2016[cited 2016 May 18]. Available from: http://www.noo.org.uk/slide_sets.
15. James FR, Wootton S, Jackson A, Wiseman M, Copson ER, Cutress RI. Obesity in breast cancer–what is the risk factor? Eur J Cancer 2015;51:705–20.
16. Westphal SA. Obesity, abdominal obesity, and insulin resistance. Clin Cornerstone 2008;9:23–9; discussion 30–1.
17. Xu WH, Matthews CE, Xiang YB, Zheng W, Ruan ZX, Cheng JR, et al. Effect of adiposity and fat distribution on endometrial cancer risk in Shanghai women. Am J Epidemiol 2005;161:939–47.
18. Ju W, Kim HJ, Hankinson SE, De Vivo I, Cho E. Prospective study of body fat distribution and the risk of endometrial cancer. Cancer Epidemiol 2015;39:567–70.
19. Aune D, Navarro Rosenblatt DA, Chan DS, Vingeliene S, Abar L, Vieira AR, et al. Anthropometric factors and endometrial cancer risk: a systematic review and dose-response meta-analysis of prospective studies. Ann Oncol 2015;26:1635–48.
20. Hosono S, Matsuo K, Hirose K, Ito H, Suzuki T, Kawase T, et al. Weight gain during adulthood and body weight at age 20 are associated with the risk of endometrial cancer in Japanese women. J Epidemiol 2011;21:466–73.
21. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. 1999. Biochem Biophys Res Commun 2012;425:560–4.
22. Brakenhielm E, Veitonmaki N, Cao R, Kihara S, Matsuzawa Y, Zhivotovsky B, et al. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. Proc Natl Acad Sci U S A 2004;101:2476–81.
23. Dieudonne MN, Bussiere M, Dos Santos E, Leneveu MC, Giudicelli Y, Pecquery R. Adiponectin mediates antiproliferative and apoptotic responses in human MCF7 breast cancer cells. Biochem Biophys Res Commun 2006;345:271–9.
24. Gong TT, Wu QJ, Wang YL, Ma XX. Circulating adiponectin, leptin and adiponectin-leptin ratio and endometrial cancer risk: evidence from a meta-analysis of epidemiologic studies. Int J Cancer 2015;137:1967–78.
25. Dobson R, Burgess MI, Sprung VS, Irwin A, Hamer M, Jones J, et al. Metabolically healthy and unhealthy obesity: differential effects on myocardial function according to metabolic syndrome, rather than obesity. Int J Obes 2016;40:153–61.
26. Renehan AG, Roberts DL, Dive C. Obesity and cancer: pathophysiological and biological mechanisms. Archiv Physiol Biochem 2008;114:71–83.
27. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomarkers Prev 2002;11:1531–43.
28. Siiteri PK. Steroid hormones and endometrial cancer. Cancer Res 1978;38:4360–6.
29. Dossus L, Allen N, Kaaks R, Bakken K, Lund E, Tjonneland A, et al. Reproductive risk factors and endometrial cancer: the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2010;127:442–51.
30. Wu QJ, Li YY, Tu C, Zhu J, Qian KQ, Feng TB, et al. Parity and endometrial cancer risk: a meta-analysis of epidemiological studies. Sci Rep 2015;5:14243.
31. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579–91.
32. Soini T, Hurskainen R, Grenman S, Maenpaa J, Paavonen J, Pukkala E. Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. Obstet Gynecol 2014;124:292–9.
33. American College of O, Gynecologists Committee on Gynecologic P. ACOG committee opinion. No. 336: Tamoxifen and uterine cancer. Obstet Gynecol 2006;107:1475–8.
34. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371–88.
35. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381:805–16.
36. van Leeuwen FE, Benraadt J, Coebergh JW, Kiemeney LA, Gimbrere CH, Otter R, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. Lancet 1994;343:448–52.
37. Husing A, Dossus L, Ferrari P, Tjonneland A, Hansen L, Fagherazzi G, et al. An epidemiological model for prediction of endometrial cancer risk in Europe. Eur J Epidemiol 2016;31:51–60.
38. Pfeiffer RM, Park Y, Kreimer AR, Lacey JV Jr, Pee D, Greenlee RT, et al. Risk prediction for breast, endometrial, and ovarian cancer in white women aged 50 y or older: derivation and validation from population-based cohort studies. PLoS Med 2013;10:e1001492.
39. Allen NE, Key TJ, Dossus L, Rinaldi S, Cust A, Lukanova A, et al. Endogenous sex hormones and endometrial cancer risk in women in the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr Relat Cancer 2008;15:485–97.
40. Clendenen TV, Hertzmark K, Koenig KL, Lundin E, Rinaldi S, Johnson T, et al. Premenopausal Circulating Androgens and Risk of Endometrial Cancer: results of a Prospective Study. Horm Cancer 2016;7:178–87.
41. Dallal CM, Lacey JV Jr, Pfeiffer RM, Bauer DC, Falk RT, Buist DS, et al. Estrogen metabolism and risk of postmenopausal endometrial and ovarian cancer: the B ∼ FIT cohort. Horm Cancer 2016;7:49–64.
42. Brown SB, Hankinson SE. Endogenous estrogens and the risk of breast, endometrial, and ovarian cancers. Steroids 2015;99:8–10.
43. Potischman N, Hoover RN, Brinton LA, Siiteri P, Dorgan JF, Swanson CA, et al. Case-control study of endogenous steroid hormones and endometrial cancer. J Natl Cancer Inst 1996;88:1127–35.
44. Renehan AG, Frystyk J, Flyvbjerg A. Obesity and cancer risk: the role of the insulin-IGF axis. Trends Endocrinol Metab 2006;17:328–36.
45. Nagamani M, Stuart CA. Specific binding and growth-promoting activity of insulin in endometrial cancer cells in culture. Am J Obstetrics Gynecol 1998;179:6–12.
46. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia 2007;50:1365–74.
47. Zhang ZH, Su PY, Hao JH, Sun YH. The role of preexisting diabetes mellitus on incidence and mortality of endometrial cancer: a meta-analysis of prospective cohort studies. Int J Gynecol Cancer 2013;23:294–303.
48. Nead KT, Sharp SJ, Thompson DJ, Painter JN, Savage DB, Semple RK, et al. Evidence of a causal association between insulinemia and endometrial cancer: a Mendelian randomization analysis. J Natl Cancer Inst 2015;107. pii: djv17.
49. Hernandez AV, Pasupuleti V, Benites-Zapata VA, Thota P, Deshpande A, Perez-Lopez FR. Insulin resistance and endometrial cancer risk: a systematic review and meta-analysis. Eur J Cancer 2015;51:2747–58.
50. Dossus L, Lukanova A, Rinaldi S, Allen N, Cust AE, Becker S, et al. Hormonal, metabolic, and inflammatory profiles and endometrial cancer risk within the EPIC cohort–a factor analysis. Am J Epidemiol 2013;177:787–99.
51. Lukanova A, Zeleniuch-Jacquotte A, Lundin E, Micheli A, Arslan AA, Rinaldi S, 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.
52. Singh B, Saxena A. Surrogate markers of insulin resistance: a review. World J Diabetes 2010;1:36–47.
53. Cust AE, Allen NE, Rinaldi S, Dossus L, Friedenreich C, Olsen A, 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.
54. Travier N, Jeffreys M, Brewer N, Wright CS, Cunningham CW, Hornell J, et al. Association between glycosylated hemoglobin and cancer risk: a New Zealand linkage study. Ann Oncol 2007;18:1414–9.
55. Bonadona V, Bonaiti B, Olschwang S, Grandjouan S, Huiart L, Longy M, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011;305:2304–10.
56. Barrow E, Robinson L, Alduaij W, Shenton A, Clancy T, Lalloo F, et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome:

a report of 121 families with proven mutations. Clin Genet 2009;75: 141–9.
57. Bharati R, Jenkins MA, Lindor NM, Le Marchand L, Gallinger S, Haile RW, et al. Does risk of endometrial cancer for women without a germline mutation in a DNA mismatch repair gene depend on family history of endometrial cancer or colorectal cancer? Gynecol Oncol 2014;133:287–92.
58. Schmandt RE, Iglesias DA, Co NN, Lu KH. Understanding obesity and endometrial cancer risk: opportunities for prevention. Am J Obstet Gynecol 2011;205:518–25.
59. Ye J, Keller JN. Regulation of energy metabolism by inflammation: a feedback response in obesity and calorie restriction. Aging 2010;2:361–8.
60. Linkov F, Maxwell GL, Felix AS, Lin Y, Lenzner D, Bovbjerg DH, et al. Longitudinal evaluation of cancer-associated biomarkers before and after weight loss in RENEW study participants: implications for cancer risk reduction. Gynecol Oncol 2012;125:114–9.
61. Dossus L, Rinaldi S, Becker S, Lukanova A, Tjonneland A, Olsen A, et al. Obesity, inflammatory markers, and endometrial cancer risk: a prospective case-control study. Endocr Relat Cancer 2010;17:1007–19.
62. Modugno F, Ness RB, Chen C, Weiss NS. Inflammation and endometrial cancer: a hypothesis. Cancer Epidemiol Biomarkers Prev 2005;14:2840–7.
63. Wang T, Rohan TE, Gunter MJ, Xue X, Wactawski-Wende J, Rajpathak SN, et al. A prospective study of inflammation markers and endometrial cancer risk in postmenopausal hormone nonusers. Cancer Epidemiol Biomarkers Prev 2011;20:971–7.
64. Burn J, Gerdes AM, Macrae F, Mecklin JP, Moeslein G, Olschwang S, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 2011;378:2081–7.
65. CRUK. Lifetime risk of uterine cancer; 2016[cited 2016 Oct 10]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer/incidence#heading-Five.
66. UK Biobank. UK Biobank; 2016[cited 2016 Apr 19]. Available from: http://www.ukbiobank.ac.uk/.
67. Campbell KL, Foster-Schubert KE, Alfano CM, Wang CC, Wang CY, Duggan CR, et al. Reduced-calorie dietary weight loss, exercise, and sex hormones in postmenopausal women: randomized controlled trial. J Clin Oncol 2012;30:2314–26.
68. Harvie M, Wright C, Pegington M, McMullan D, Mitchell E, Martin B, et al. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women. Br J Nutr 2013;110:1534–47.
69. Prentice RL, Thomson CA, Caan B, Hubbell FA, Anderson GL, Beresford SA, et al. Low-fat dietary pattern and cancer incidence in the Women's Health Initiative dietary modification randomized controlled trial. J Natl Cancer Inst 2007;99:1534–43.
70. Parker ED, Folsom AR. Intentional weight loss and incidence of obesity-related cancers: the Iowa Women's Health Study. Int J Obes Relat Metab Disord 2003;27:1447–52.
71. McTiernan A. Mechanisms linking physical activity with cancer. Nat Rev Cancer 2008;8:205–11.
72. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. Eur J Cancer 2010;46:2593–604.
73. Schmid D, Behrens G, Keimling M, Jochem C, Ricci C, Leitzmann M. A systematic review and meta-analysis of physical activity and endometrial cancer risk. Eur J Epidemiol 2015;30:397–412.
74. Ashrafian H, Ahmed K, Rowland SP, Patel VM, Gooderham NJ, Holmes E, et al. Metabolic surgery and cancer: protective effects of bariatric procedures. Cancer 2011;117:1788–99.
75. Ashrafian H, le Roux CW, Rowland SP, Ali M, Cummin AR, Darzi A, et al. Metabolic surgery and obstructive sleep apnoea: the protective effects of bariatric procedures. Thorax 2012;67:442–9.
76. Argenta P, Svendsen C, Elishaev E, Gloyeske N, Geller MA, Edwards RP, et al. Hormone receptor expression patterns in the endometrium of asymptomatic morbidly obese women before and after bariatric surgery. Gynecol Oncol 2014;133:78–82.
77. Adams TD, Hunt SC. Cancer and obesity: effect of bariatric surgery. World J Surg 2009;33:2028–33.
78. Zhang Q, Celestino J, Schmandt R, McCampbell AS, Urbauer DL, Meyer LA, et al. Chemopreventive effects of metformin on obesity-associated endometrial proliferation. Am J Obstetrics Gynecol 2013;209:24.e1–e12.
79. Xie Y, Wang YL, Yu L, Hu Q, Ji L, Zhang Y, et al. Metformin promotes progesterone receptor expression via inhibition of mammalian target of rapamycin (mTOR) in endometrial cancer cells. J Steroid Biochem Mol Biol 2011;126:113–20.
80. Hattori Y, Suzuki K, Hattori S, Kasai K. Metformin inhibits cytokine-induced nuclear factor kappaB activation via AMP-activated protein kinase activation in vascular endothelial cells. Hypertension 2006;47:1183–8.
81. Legro RS, Zaino RJ, Demers LM, Kunselman AR, Gnatuk CL, Williams NI, et al. The effects of metformin and rosiglitazone, alone and in combination, on the ovary and endometrium in polycystic ovary syndrome. Am J Obstet Gynecol 2007;196:402e1–10; discussion e10–1.
82. Shen ZQ, Zhu HT, Lin JF. Reverse of progestin-resistant atypical endometrial hyperplasia by metformin and oral contraceptives. Obstet Gynecol 2008;112:465–7.
83. Session DR, Kalli KR, Tummon IS, Damario MA, Dumesic DA. Treatment of atypical endometrial hyperplasia with an insulin-sensitizing agent. Gynecol Endocrinol 2003;17:405–7.
84. Soffer D, Shi J, Chung J, Schottinger JE, Wallner LP, Chlebowski RT, et al. Metformin and breast and gynecological cancer risk among women with diabetes. BMJ Open Diabetes Res Care 2015;3:e000049.
85. Hannaford PC, Iversen L, Macfarlane TV, Elliott AM, Angus V, Lee AJ. Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study. BMJ 2010;340:c927.
86. Lu KH, Loose DS, Yates MS, Nogueras-Gonzalez GM, Munsell MF, Chen LM, et al. Prospective multicenter randomized intermediate biomarker study of oral contraceptive versus depo-provera for prevention of endometrial cancer in women with Lynch syndrome. Cancer Prev Res 2013;6:774–81.
87. Collaborative Group on Epidemiological Studies of Ovarian C,Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet 2008;371:303–14.
88. Kwon JS, Lu KH. Cost-effectiveness analysis of endometrial cancer prevention strategies for obese women. Obstet Gynecol 2008;112:56–63.
89. Bahamondes L, Valeria Bahamondes M, Shulman LP. Non-contraceptive benefits of hormonal and intrauterine reversible contraceptive methods. Hum Reprod Update 2015;21:640–51.
90. Wan YL, Holland C. The efficacy of levonorgestrel intrauterine systems for endometrial protection: a systematic review. Climacteric 2011;14:622–32.
91. Verdoodt F, Friis S, Dehlendorff C, Albieri V, Kjaer SK. Non-steroidal anti-inflammatory drug use and risk of endometrial cancer: a systematic review and meta-analysis of observational studies. Gynecol Oncol 2016;140:352–8.
92. McIlhatton MA, Tyler J, Burkholder S, Ruschoff J, Rigas B, Kopelovich L, et al. Nitric oxide-donating aspirin derivatives suppress microsatellite instability in mismatch repair-deficient and hereditary nonpolyposis colorectal cancer cells. Cancer Res 2007;67:10966–75.
93. Garland CF, Garland FC, Gorham ED, Lipkin M, Newmark H, Mohr SB, et al. The role of vitamin D in cancer prevention. Am J Public Health 2006;96:252–61.
94. Liu JJ, Bertrand KA, Karageorgi S, Giovannucci E, Hankinson SE, Rosner B, et al. Prospective analysis of vitamin D and endometrial cancer risk. Ann Oncol 2013;24:687–92.
95. Yu W, Cline M, Maxwell LG, Berrigan D, Rodriguez G, Warri A, et al. Dietary vitamin D exposure prevents obesity-induced increase in endometrial cancer in Pten+/− mice. Cancer Prev Res 2010;3:1246–58.
96. Ferrini RL, Barrett-Connor E. Caffeine intake and endogenous sex steroid levels in postmenopausal women. The Rancho Bernardo Study. Am J Epidemiol 1996;144:642–4.
97. Loopstra-Masters RC, Liese AD, Haffner SM, Wagenknecht LE, Hanley AJ. Associations between the intake of caffeinated and decaffeinated coffee and measures of insulin sensitivity and beta cell function. Diabetologia 2011;54:320–8.
98. Bohn SK, Blomhoff R, Paur I. Coffee and cancer risk, epidemiological evidence, and molecular mechanisms. Mol Nutr Food Res 2014;58:915–30.
99. Zhou Q, Luo ML, Li H, Li M, Zhou JG. Coffee consumption and risk of endometrial cancer: a dose-response meta-analysis of prospective cohort studies. Sci Rep 2015;5:13410.

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