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# **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 rising 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. Based on 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 cut-off 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 rising tide of endometrial cancer is to be stemmed.

## **Introduction**

Endometrial cancer is the fourth most common cancer in women in the UK, with over 9000 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 rise 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 3700 new cases of endometrial cancer diagnosed each year in the UK [figure 1] (3, 4). In line with this, mortality rates are also rising, albeit to a lesser extent, with a further 850 endometrial cancer deaths per year anticipated in England and Wales alone by 2030 (3). Whilst 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 rising tide of endometrial cancer if the effects, both for individual patients and 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 trialled to maximise 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 histological subtype [75% of all endometrial cancers] (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 realised. Experimental and epidemiological evidence will be used to argue for the inclusion of measures of obesity (obesity score), unopposed oestrogen 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.

There are two limitations to this approach, which must be appreciated at the outset. Whilst such a model is likely to have maximal impact on disease burden, it may not significantly reduce endometrial cancer mortality as non-endometrioid tumours 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 (O)**

Any risk prediction model for endometrial cancer will be centred 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 tumour types (6, 7). Several underlying mechanisms linking excess adiposity and endometrial cancer have been described; excess oestrogen production, insulin resistance and inflammation (figure 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)<sup>2</sup>.

## **BMI**

Meta-analyses of prospective observational studies have shown that a  $5\text{kg}/\text{m}^2$  increase in BMI is associated with a 60% increase in the relative risk of developing endometrial cancer (6, 8). The effect is non-linear though, with a proportionally greater increase in risk for each  $5\text{kg}/\text{m}^2$  rise in BMI above  $27\text{kg}/\text{m}^2$ , such that a woman with a BMI of  $42\text{kg}/\text{m}^2$  has a 9.11 times (95% CI 7.26-11.51) greater risk of developing endometrial cancer than a woman with a BMI of  $22\text{kg}/\text{m}^2$  (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  $\geq 40\text{kg}/\text{m}^2$  along with additional risk factors for the disease). It is already known that there is a not insignificant prevalence of asymptomatic endometrial hyperplasia of 8.6-10% in the bariatric surgery population [women with BMI  $\geq 40\text{kg}/\text{m}^2$  or BMI  $\geq 35\text{kg}/\text{m}^2$  in the presence of obesity-related co-morbidities, such as diabetes mellitus or obstructive sleep apnoea] (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 apnoea (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 ( $\geq 40\text{kg}/\text{m}^2$ ), 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 vs. peripheral obesity can, therefore, be useful to further 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 non-significant increase in endometrial cancer risk with each 0.1-unit increase in waist:hip ratio [RR 1.07, 95% CI 0.97-1.17] (19). Individually, however, both waist and hip circumference were independently associated with disease risk (RR 2.16 and 1.30 per 10cm 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**

Whilst 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 18-20 years and middle age was associated with a higher endometrial cancer risk, even after adjusting for current BMI (19). For each 5kg increase in weight over this time period, the risk of endometrial cancer rose 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, though levels are inversely correlated with BMI (21). Biologically, it has an anti-cancer effect, acting as an anti-inflammatory and improving insulin sensitivity, whilst inhibiting angiogenesis and downregulating vascular adhesion molecule expression (22). This is achieved through activation of AMPK and inactivation of ERK and MAPK (figure 2). It is also able to increase apoptosis by inducing expression of p53 and Bax, thereby acting as a negative regulator of tumour 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 5µg/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 HRT use. This supports the distinction between 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 tumour formation, including proinflammatory, proangiogenic, mitogenic and anti-apoptotic effects, through activation of *MAPK*, *PI3K* and *STAT*



pathways and increases in aromatase activity (26). Whilst a meta-analysis of observational studies found that women with leptin levels in the upper tertile had a two-fold increase in their risk of endometrial cancer compared to those with the lowest levels, independent of BMI, the included studies were heterogeneous in design and inclusion criteria and insufficient data was 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 epidemiological and *in vitro* evidence demonstrating a dose-response relationship between excess adiposity and endometrial cancer risk. Whilst they are included to measure different aspects of this association, in order 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 (R)**

Established reproductive risk factors for endometrial cancer can be interpreted in light of the 'unopposed oestrogen theory'. Oestrogen induces endometrial proliferation through local production of insulin-like growth factor-1 (IGF-1), increasing the risk of accumulation of genetic mutations in proto-oncogenes and tumour 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 oestrogen, through early menarche (<12 years) or late menopause (≥55 years) is, not surprisingly, associated with an increased risk of endometrial cancer (28). Whilst oestrogen only HRT is a time-honoured 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 COCP for ≥ 5 years is associated with a significant reduction in endometrial cancer risk due to suppression of endogenous oestrogen 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 that had had one child had a 27% lower risk of developing endometrial cancer (RR 0.73 95%CI 0.64-0.84) and those with two children a 38% reduction in endometrial cancer risk (RR 0.62, 95%CI 0.53-0.74) (30). Whilst there was some evidence of a dose response relationship between parity and endometrial cancer risk, the numbers of included women with three or more children were too small to draw meaningful conclusions from.

For postmenopausal women, adipose tissue becomes the dominant source of oestrogen, responsible for the conversion of androstenedione and testosterone into oestrogen and oestradiol by aromatase and 17 $\beta$ -hydroxysteroid dehydrogenase (17 $\beta$ -HSD) produced by adipocytes (28, 31). Obesity hence plays a significant role in postmenopausal oestrogen production and also increases its bioavailability by reducing sex hormone binding globulin production (figure 2).

Increased oestrogen 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 oestrogen by increasing synthesis of insulin-like growth factor binding protein-1 (IGFBP-1) to mop up excess IGF-1 and promoting expression of the oestrogen sulfo-transferase and 17 $\beta$ -HSD enzymes, to convert oestradiol into the less potent oestrone (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<sup>®</sup>) have a significantly lower risk of endometrial cancer compared with non-users [standardized incidence ratio 0.46, 95% CI 0.33-0.64] (32).

Tamoxifen, a selective oestrogen 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 2-3-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, though 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, Park (38) found a significant over-prediction 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 epidemiological 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). Whilst there is insufficient data available in the literature to determine optimal cut-off values, free testosterone levels of > 17pmol/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 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 pre-menopausal endometrial cancer as the study by

Clendenen, Hertzmark (40) found no association if a diagnosis was made prior to the age of 55 years, though 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 oestrogen production in postmenopausal women and PCOS in younger individuals (40).

Measurement of serum oestrogen 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 oestrogen in postmenopausal women with endometrial cancer compared with controls, with oestradiol levels in the upper tertile being associated with a 2-4 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, though as levels vary dramatically throughout the menstrual cycle, attempting to control for this would be difficult (27).

### **Insulin risk score (I)**

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 (figure 2). Insulin and IGF-1 also stimulate  $\beta$ -catenin, a signalling pathway involved in early tumour 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 tumour promoting capacity. Beyond these direct effects, hyperinsulinemia is also involved in increasing ovarian androgen production and peripheral

aromatisation to oestrogen, 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 two fold elevation in endometrial cancer risk, even after adjustment for activity levels and BMI (46). Similarly, PCOS, whilst featuring in the reproductive risk score because of its link with hyper-androgenaemia, is also included in the insulin risk score; 50-70% of patients with PCOS are also insulin resistant and this group have a particularly high endometrial cancer risk (47). Despite the epidemiological 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 standardised protocol for sample preparation and testing and the absence of validated cut-off 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 euglycaemic clamp test, but this is too expensive and time-consuming to be used apart from on an individual patient basis (52). Whilst 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 two 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 compared with 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 0.76nmol/l is associated with 1.5-2 fold elevation in endometrial cancer risk and is used in the model (53).

Glycosylated haemoglobin (HbA1C) is now part of both the World Health Organisation (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 glycaemic control over a preceding 8-12 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 cut-off values for inclusion here (54). It did suggest, though, that even modest elevations in HbA1C in non-diabetic patients may significantly increase cancer risk. Further work is clearly warranted in this area.

### **Genetic risk score (G)**

The risk of endometrial cancer in women with Lynch syndrome (mutations in the DNA mismatch repair genes MSH2, 6, MLH1, PMS2 or EPCAM) is significantly elevated, with a cumulative risk of endometrial cancer of 16-71% 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.

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,  $p < 0.001$ ](57). This risk is increased further if two 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. Whilst 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**

Whilst not directly incorporated at present, future work may well see measures of inflammation feature in the risk prediction model. Adipose tissue is increasingly being recognised 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 characterised by chronic inflammation (59). Cytokines are produced by activated adipocytes and infiltrating macrophages in response to adipose tissue expansion and localised hypoxia. Increasing BMI and waist circumference are associated with elevated levels of cytokines including interferons, IL-6, IL-8, interleukin-1 receptor antagonist (IL-1Ra) and C-reactive peptide [CRP] (26, 60, 61).

Endometrial carcinogenesis may be promoted by this inflammatory milieu. Chronic inflammation results in the generation of free radicals, increased concentrations of COX-2 and prostaglandin E2 and leads to cell proliferation and DNA damage (62). Activation of the NFkB 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 tumour formation (figure 2). Inflammation also contributes to the development of insulin resistance and IL-6 stimulates aromatase activity and the conversion of

androgens into oestrogen 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, though 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 non-specific to be used in a risk prediction model; levels are elevated transiently in numerous situations, including sub-clinical infection. Longitudinal, prospective cohort studies are required to evaluate the role of inflammatory cytokines, such as IL-6 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 four 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, figure 3). Based on an absolute lifetime risk of the disease of 2.4%, this approximates to an absolute risk of endometrial cancer of up to 4.9%, 7.3-17.1% and  $\geq 19.5\%$  for the low, medium and high risk groups, respectively (65). The predominant risk factor identified can be used to determine the type of prophylactic intervention trialled, for example, metformin when the insulin score is particularly high, the combined oral contraceptive pill 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, in order 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, though 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  $>25\text{kg/m}^2$ . 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 individualised 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 behaviour 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<sup>®</sup>, 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 hypoglycaemic medication indicated if glycaemic control cannot be optimised 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 five 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 epidemiological 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 is available. This will allow the model to be refined, using random decision forests and unconditional logistic regression, in order to optimise 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 over 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 organisation 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 would also potentially guide the development of prophylactic treatment aimed at specific disease causing targets, such as insulin resistance and inflammation.

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## Display items

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

Intervention	Target population	Mechanism of action	Current evidence	Side effects	Contraindications	Potential problems
Low fat diet ( $\leq 20\%$ of energy from fat)	BMI $>30\text{kg/m}^2$	<ul style="list-style-type: none"> <li>• Decrease adiposity and weight</li> <li>• Decrease serum oestrone, oestradiol and testosterone levels (68)</li> <li>• Increase sex hormone binding globulin levels (68)(68)(68)(68)(68)(68)(68)(68)</li> <li>• Improved insulin sensitivity (69)</li> </ul>	<ul style="list-style-type: none"> <li>• Low fat diets <i>per se</i> do not prevent endometrial cancer if they are not associated with significant weight loss (70)</li> <li>• Self-reported prior weight loss of 20lbs or more in a single episode associated with a non-significant 7% reduction in risk of endometrial cancer (71)</li> <li>• Lower insulin and HOMA-IR levels found after 3 months of an intermittent fasting diet, where only 600-650 cal/day are consumed on two days a week, 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 (69). No studies of the effect of intermittent fasting on cancer prevention in humans have yet been published.</li> </ul>	Nil	Nil	<ul style="list-style-type: none"> <li>• Long term compliance often low with weight gain noted after discontinuing intervention.</li> <li>• Excessive rebound weight gain may exacerbate endometrial cancer risk</li> </ul>
Physical activity	BMI $\geq 25\text{kg/m}^2$	<ul style="list-style-type: none"> <li>• Decrease adiposity and weight</li> <li>• Improve insulin sensitivity and reduce insulin levels (72)</li> <li>• Reduce serum oestradiol and increase sex hormone binding globulin levels (72)</li> <li>• May improve innate and acquired immune response (72)</li> </ul>	<ul style="list-style-type: none"> <li>• 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 (73). 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 (74).</li> <li>• No clinical trials undertaken looking</li> </ul>	Nil	Other co-morbidities limiting exercise capacity	<ul style="list-style-type: none"> <li>• No consensus reached on from what age physical activity is beneficial or for how long it needs to be maintained.</li> <li>• Compliance likely to be lower if long term intervention required.</li> </ul>

			at increasing physical activity as a primary prophylactic intervention against endometrial cancer			
Bariatric surgery	BMI $\geq 40\text{kg/m}^2$ or $\geq 35\text{kg/m}^2$ in the presence of obesity-related co-morbidities, e.g. diabetes, obstructive sleep apnoea	<ul style="list-style-type: none"> <li>• Decrease adiposity and weight (either through calorie restriction, malabsorption or decrease in appetite)</li> <li>• Improvement in insulin sensitivity (75)</li> <li>• Decrease in oxidative stress and inflammation (76)</li> <li>• Lowering leptin levels and increase in adiponectin (75)</li> <li>• Decrease sex steroid levels and normalise endometrial hormone receptor expression (77)</li> </ul>	<ul style="list-style-type: none"> <li>• 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, 78).</li> <li>• Benefit still remains, albeit smaller, for those who fail to lose weight after the procedure (12)</li> </ul>	<ul style="list-style-type: none"> <li>• Surgical complications, including anastomotic leak</li> <li>• Malabsorption (depending upon type of surgical procedure)</li> <li>• Risk of perioperative mortality</li> </ul>	<ul style="list-style-type: none"> <li>• Patient not motivated to undergo procedure</li> <li>• Medically unfit to undergo surgical procedure</li> <li>• Alcohol or substance misuse</li> <li>• Uncontrolled psychiatric problems</li> </ul>	<ul style="list-style-type: none"> <li>• Estimated that 71 bariatric procedures would need to be conducted to prevent 1 incident endometrial cancer, though patients would also benefit from resolution of diabetes and improvements in cardiovascular disease (78)</li> <li>• May only be cost-effective for those at greatest endometrial cancer risk</li> <li>• Requires patient to be motivated to adapt dietary pattern</li> </ul>
Metformin	<ul style="list-style-type: none"> <li>• Insulin resistant-HOMA-IR <math>&gt;2.8</math></li> <li>• Polycystic ovary syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Improve insulin sensitivity and lower insulin levels</li> <li>• Reduction in oestrogen-stimulated expression of proto-oncogenes c-fos and c-myc in animal studies (79)</li> <li>• Increase in endometrial progesterone receptor expression (80)</li> <li>• Inhibition of TNF-<math>\alpha</math> signalling, at least in vascular endothelial cells (81)</li> </ul>	<ul style="list-style-type: none"> <li>• 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 (82-84).</li> <li>• Difficult to determine whether benefit solely due to metformin though as some women co-treated with COCP (83)</li> </ul>	GI upset- nausea/vomiting, diarrhoea Rash	Severe renal disease Severe liver disease Alcohol abuse	<ul style="list-style-type: none"> <li>• Identifying insulin resistant population difficult due to lack of standardisation of testing</li> <li>• No benefit in terms of endometrial cancer risk reduction seen for diabetic patients</li> </ul>

						taking metformin with the aim of lowering serum glucose (85)
Combined oral contraceptive pill (COCP)	<ul style="list-style-type: none"> <li>• Polycystic ovary syndrome (PCOS)</li> <li>• Oligomenorrhoea</li> <li>• Lynch syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Reduction in endometrial proliferation</li> </ul>	<ul style="list-style-type: none"> <li>• Ever use of COCP associated with a 40-50% reduction in endometrial cancer risk, with benefit continuing even after discontinuation of use (29, 86)</li> <li>• 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 (87)</li> <li>• Additional benefit of reducing ovarian cancer risk by 20% for each 5 years of use (88)</li> </ul>	Headache, breast tenderness, breakthrough bleeding, increased risk of venous thromboembolism, increased risk of breast and cervical cancer (risk returns to normal once use discontinued)	Pre-existing cardiovascular disease, family history of thrombosis, morbid obesity, smoker age >35 years	Decision analytical model suggested that 5 years of COCP use in obese women was unlikely to be a cost effective strategy for decreasing endometrial cancer incidence, though 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 (89)
Levonorgestrel-releasing intrauterine system (Mirena®)	<ul style="list-style-type: none"> <li>• Tamoxifen users</li> <li>• Oestrogen-only HRT users</li> <li>• Obese women</li> </ul>	<ul style="list-style-type: none"> <li>• Downregulation of endometrial oestrogen receptors and reduction in cellular proliferation (90)</li> </ul>	<ul style="list-style-type: none"> <li>• Use of levonorgestrel-releasing intrauterine system for the treatment of heavy menstrual bleeding associated with a 54% reduction in endometrial cancer compared with pre-menopausal 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.</li> <li>• Use associated with protection against endometrial hyperplasia in tamoxifen and oestrogen-only HRT users (91)</li> </ul>	Irregular bleeding (usually settles within 6 months), 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

			<ul style="list-style-type: none"> <li>• Current on-going study by our own group investigating the role of the levonorgestrel-releasing intrauterine system in the primary prevention of endometrial cancer in obese women</li> </ul>			
Aspirin	BMI $\geq 30 \text{kg/m}^2$	<ul style="list-style-type: none"> <li>• Anti-inflammatory effect</li> <li>• Reduction in aromatase and oestrogen levels (61)</li> <li>• Increased apoptosis (62)</li> </ul>	<ul style="list-style-type: none"> <li>• Meta-analysis of observational studies found a small, non-significant reduction in endometrial cancer risk with long term aspirin in the general population (92).</li> <li>• Obese women may derive greater benefit, though.</li> <li>• 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 (67)</li> </ul>	Indigestion, gastrointestinal bleeding, peptic ulcer	Bleeding disorders, allergy to non-steroidal 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
Vitamin D	BMI $\geq 30 \text{kg/m}^2$	<ul style="list-style-type: none"> <li>• Inhibition of cell proliferation</li> <li>• Reduction in angiogenesis (93)</li> </ul>	<ul style="list-style-type: none"> <li>• No association between vitamin D levels and total dietary vitamin D intake and endometrial cancer risk (94).</li> <li>• Evidence of a benefit from vitamin D supplementation limited to animal studies using obese Pten (+/-) mice (95)</li> </ul>	None with doses up to 1000IU/day high doses-bone demineralisation, hypercalcaemia	Primary hyperparathyroidism, hypercalcaemia, caution if taking digoxin	<ul style="list-style-type: none"> <li>• No evidence of benefit in general population.</li> <li>• Further studies required to determine whether vitamin D supplementation effective in obese women particularly in reducing endometrial cancer risk</li> </ul>
Coffee consumption ( $\geq 4$ cups of coffee/day)	Non/low coffee consumers	<ul style="list-style-type: none"> <li>• Increase sex hormone binding globulin levels (96)</li> <li>• Improve insulin sensitivity (97)</li> </ul>	<ul style="list-style-type: none"> <li>• Increased coffee consumption associated with lower endometrial cancer risk.</li> <li>• Seven percent reduction in</li> </ul>	Insomnia, restlessness, tachycardia, headache,	Cardiac problems, particularly arrhythmias	<ul style="list-style-type: none"> <li>• Potential confounding of results from case-control studies</li> </ul>

		<ul style="list-style-type: none"> <li>• Inhibit oxidative damage, anti-inflammatory effect</li> <li>• Induction of cellular defences and DNA repair</li> <li>• Detoxification of potential carcinogens (98)</li> </ul>	<p>endometrial cancer risk with each 1 additional cup of caffeinated coffee drunk per day and 4% reduction with de-caffeinated coffee (99). Benefit restricted to women with BMI &gt;25kg/m<sup>2</sup> and those who have never used hormone therapy.</p> <ul style="list-style-type: none"> <li>• No studies investigating coffee drinking specifically for endometrial cancer prophylaxis</li> </ul>	nausea/vomiting (related to caffeine)		<p>cannot be excluded</p> <ul style="list-style-type: none"> <li>• Side effects likely to limit number of cups of coffee that can be consumed each day</li> </ul>
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**Table 2. Proposed endometrial cancer risk prediction model.** 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.

Risk score	Risk factor	-2	-1	0	1	2	4	8
<b>Obesity</b>	BMI			<25kg/m <sup>2</sup>	25-30kg/m <sup>2</sup>	30-35kg/m <sup>2</sup>	35-40kg/m <sup>2</sup>	≥40kg/m <sup>2</sup>
	Waist circumference			<90cm	90-100cm	100-110cm	>110cm	
	Weight gain between 18-25 years and 45-55 years			<5kg	5-20kg	>20kg		
	Adiponectin	>5µg/ml		<5µg/ml				
<b>Reproductive</b>	Early menarche (<12 yrs) OR late menopause (>55 yrs)  OR Anovulation (6 months of more, unrelated to pregnancy, breast feeding or contraceptive use)			None	One or more			
	Parity	2+	1	0				
	COCP use	≥5 years		Never or <5 years				
	Ever use of tamoxifen			No		Yes		
	Free testosterone			≤17pmol/l	>17pmol/l			
<b>Insulin</b>	Type 2 diabetes			Absent		Present		
	PCOS			Absent			Present	
	C-peptide (non-fasting)			≤0.76nmo l/l		>0.76nmo l/l		
<b>Genetic</b>	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

### **Figure Legends**

**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 3700 new cases diagnosed each year in England and Wales and 850 further deaths from the disease.

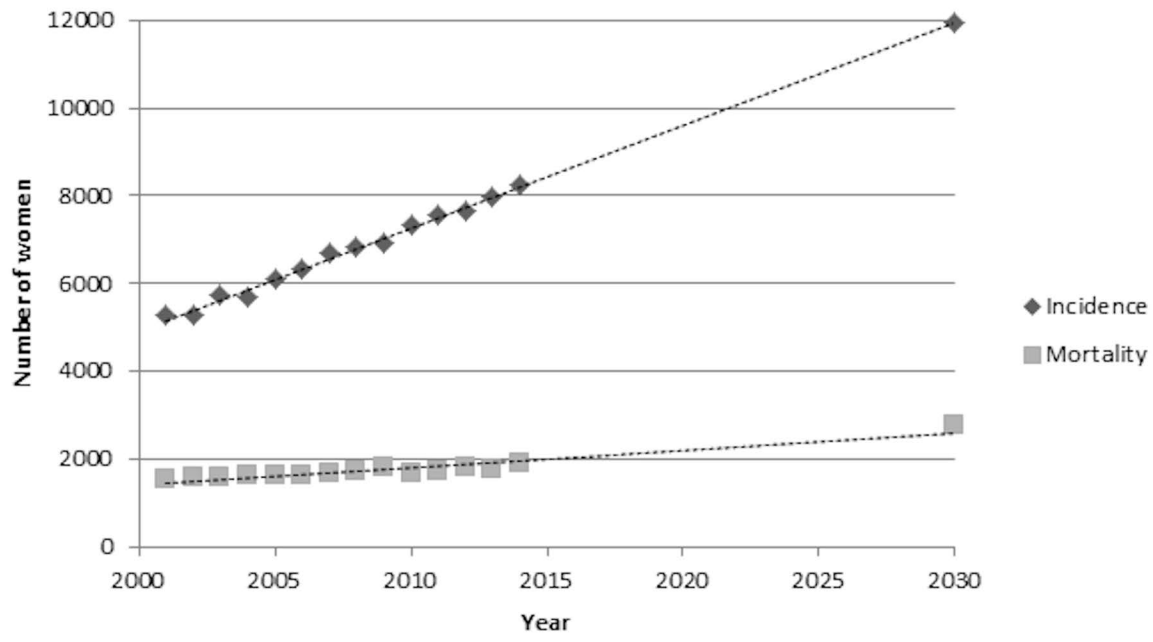
**Figure 2. Summary of pathways linking obesity with endometrial cancer development.** Obesity contributes to endometrial carcinogenesis through three separate, but closely interconnected, mechanisms; aromatisation of androgens into pro-proliferative oestrogens, an increase in local production of the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

**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, whilst 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.



1

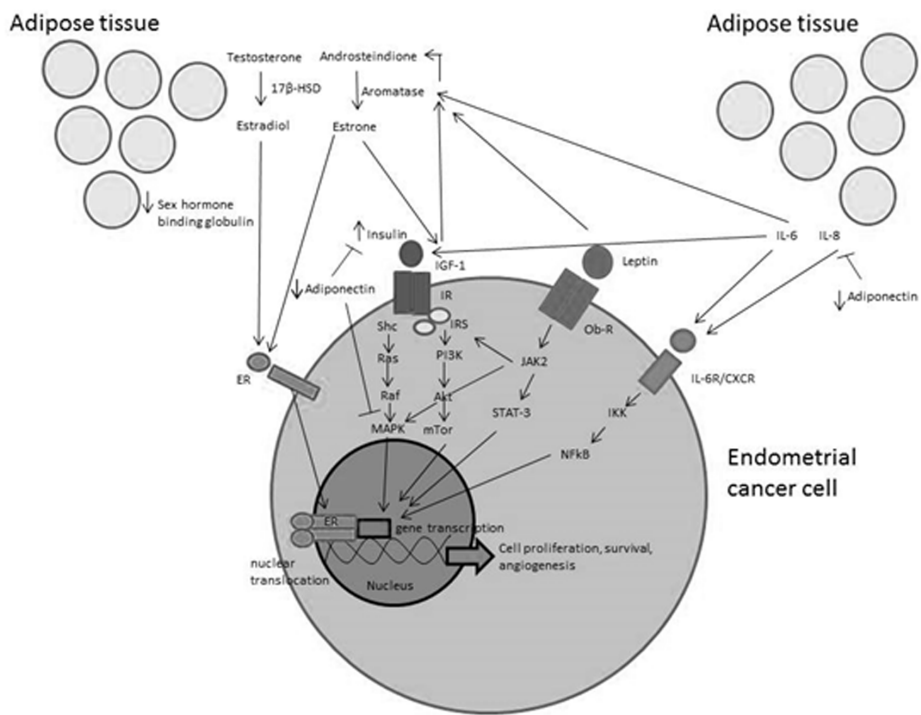
## Observed and predicted endometrial cancer incidence and mortality in England and Wales



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

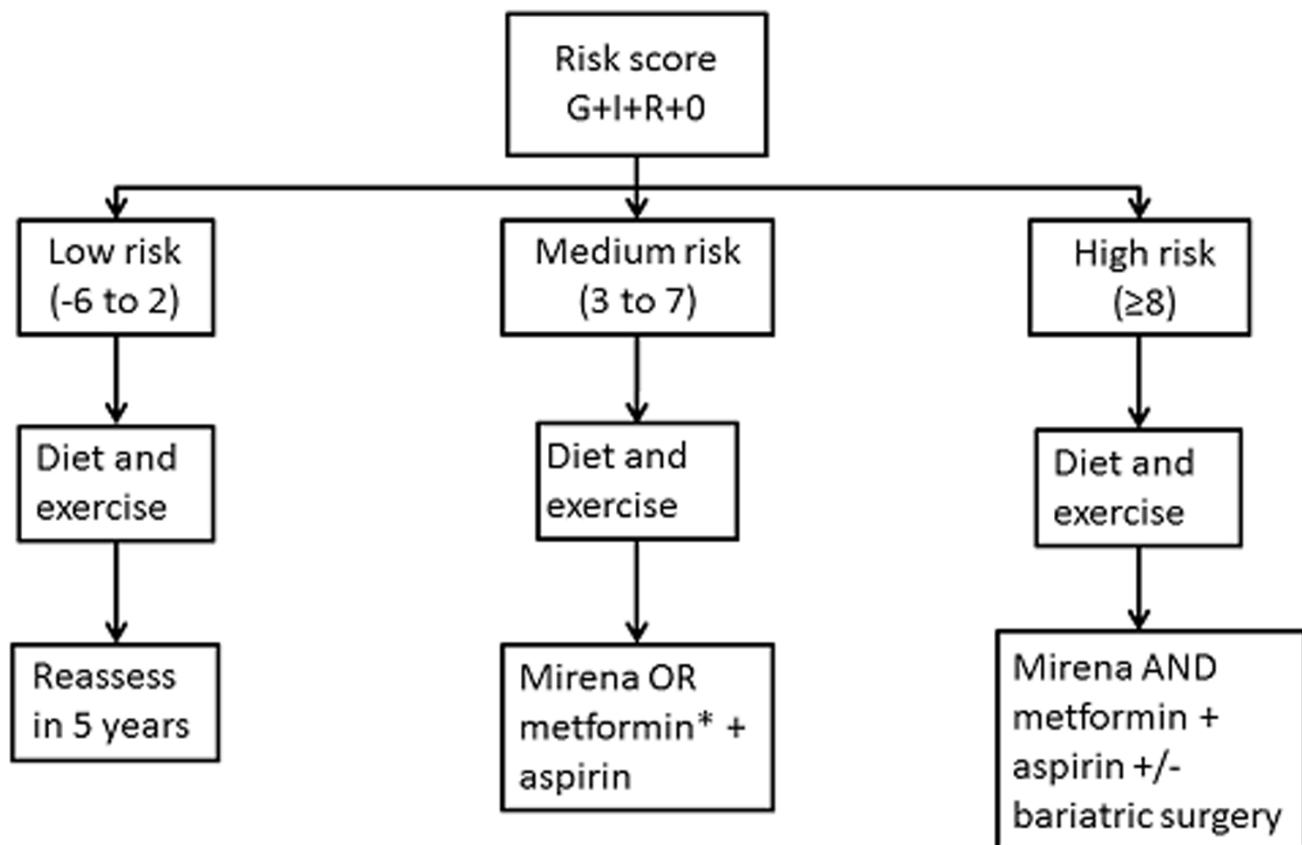
..... predicted number of cases based upon current trajectory

2



Abbreviations: 17 $\beta$ -hydroxysteroid dehydrogenase (17 $\beta$ -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), I $\kappa$ B kinase (IKK), insulin receptor (IR), oestrogen receptor (ER)

3



\*depending on whether highest score in R or I