U.PORTO

Mestrado Integrado em Medicina

Polycystic Ovary Syndrome: obesity as a determining factor for endometrial cancer risk

Inês Isabel Rodrigues Dias de Sousa

M

2022

Polycystic Ovary Syndrome: obesity as a determining factor for endometrial cancer risk

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Estudante: Inês Isabel Rodrigues Dias de Sousa

6º ano do Mestrado Integrado em Medicina

Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

Endereço de correio eletrónico: inesisabel.rds@gmail.com

Orientadora: Drª. Márcia Sofia Alves Caxide e Abreu Barreiro

Assistente Hospitalar Graduada de Ginecologia/Obstetrícia no Centro Materno Infantil do Norte – Centro de Procriação Medicamente Assistida. Licenciada em Medicina.

Professora assistente convidada do Instituto de Ciências Biomédicas Abel Salazar

Coorientador: Prof. Dr. Hélder Bruno Carvalho Ferreira

Assistente Hospitalar Graduado de Ginecologia/Obstetrícia no Centro Materno Infantil do Norte – Departamento da Mulher e da Medicina Reprodutiva. Doutorado em Medicina.

Professor auxiliar convidado do Instituto de Ciências Biomédicas Abel Salazar

Porto, junho de 2022

Porto, junho de 2022

Estudante

Inês Isabel Rodrigues Dias de Sousa

Orientadora

Coorientador

AGRADECIMENTOS

À minha orientadora e coorientador, Dra. Márcia Barreiro e Prof. Dr. Hélder Ferreira, pela orientação, colaboração e partilha de conhecimentos, que permitiram a concretização deste trabalho.

À Dra. Ana Andrade pela colaboração no desenvolvimento deste projeto e pelo apoio e disponibilidade constantes, sem os quais não seria possível a conclusão deste trabalho.

À minha família, amigos e namorado, pelo apoio incondicional, força, motivação e compreensão que me mostraram ao longo deste percurso.

RESUMO

Introdução: A Síndrome do Ovário Poliquístico (SOP) é frequentemente mencionada como um fator de risco para o desenvolvimento de cancro do endométrio, no entanto, a maioria dos estudos publicados não considera o efeito confundidor da obesidade, um fator de risco bem estabelecido para cancro do endométrio e altamente prevalente em mulheres com SOP.

Objetivos: Clarificar a extensão da influência da SOP no risco de desenvolvimento de cancro do endométrio, considerando o fator confundidor que é o Índice de Massa Corporal (IMC).

Metodologia: Foi conduzida uma revisão sistemática da literatura nas plataformas PubMed, Scopus e Web of Science, usando termos de pesquisa de forma a abranger todos os estudos que examinassem a associação entre a SOP e o cancro do endométrio. Os estudos foram considerados elegíveis para inclusão caso reportassem valores de risco de cancro do endométrio em mulheres com SOP, ajustados ao IMC.

Resultados: Na presente revisão sistemática foram incluídos 5 artigos, mais precisamente 3 estudos de coorte e 2 estudos caso-controlo**.** Um estudo encontrou um risco estatisticamente significativo de cancro do endométrio associado à SOP quando considerado o IMC. Outro estudo reportou uma atenuação do aumento de risco de cancro do endométrio após ajuste pelo IMC, em mulheres com menos de 50 anos. Os restantes três estudos não reportaram diferenças estatisticamente significativas entre valores de risco após ajuste pelo IMC.

Conclusões: O risco de cancro do endométrio em mulheres com SOP parece diminuir ou ser equivalente ao risco de mulheres sem SOP quando o ajuste aos valores de IMC é realizado. As diferenças no estabelecimento do diagnóstico da SOP traduzem-se em heterogeneidade dos achados e dificuldade na comparação dos resultados. O contributo da SOP para o risco de cancro do endométrio é possivelmente menor do que o esperado previamente.

Palavras-chave: Síndrome do Ovário Poliquístico; cancro do endométrio; excesso de peso; obesidade; estrogénios; progesterona

ABSTRACT

Introduction: Although Polycystic Ovary Syndrome (PCOS) is commonly referred to as a risk factor for endometrial cancer (EC), most of the previous studies do not consider the confounding effect of obesity, a well-known risk factor for EC that is highly prevalent in women with PCOS.

Objectives: This article aimed at clarifying the extent of the influence of PCOS on the risk of developing EC, accounting for the confounding factor of body-mass index (BMI).

Methods: A systematic review was conducted on PubMed, Scopus and Web of Science using search terms for all studies examining the association between PCOS and EC. Studies were eligible for inclusion if they reported EC risk values in women with PCOS adjusted for BMI.

Results: Five articles, including 3 cohort studies and 2 case-control studies were included in the review. One study found a statistically significant increased risk of EC associated with PCOS after adjustment for BMI. One study found an attenuation of increased EC risk after BMI adjustment in women younger than 50 years. The remaining three studies didn´t report statistically significant differences in risk after adjustment for BMI.

Conclusions: EC risk in women with PCOS appears to decrease or be equal to the EC risk of non-PCOS women when adjustment for BMI is performed. Differences in establishing PCOS diagnosis across studies translates to heterogeneous findings and difficulty comparing results. The contribution of PCOS alone to EC risk is possibly smaller than previously thought.

Keywords: Polycystic ovary syndrome; endometrial cancer; overweight; obesity; estrogen; progesterone

LIST OF ABBREVIATIONS

AR	Androgen receptors
BMI	Body-mass Index
CI	Confidence Interval
CRP	C-reactive Protein
DNA	Deoxyribonucleic acid
EC	Endometrial Cancer
ESHRE/ASRM	European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine
GI	Glycemic Index
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IGF-1	Insulin-like Growth Factor-1
IL-6	Interleukin-6
IL-8	Interleukin-8
IR	Insulin Resistance
OC	Oral contraceptives
OR	Odds Ratio
OS	Oxidative stress
PCO	Polycystic Ovaries
PCOS	Polycystic Ovary Syndrome
PI3K	Phosphatidylinositol 3-Kinase
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
RCT	Randomized Controlled Trial
RR	Rate Ratio
SHBG	Sex Hormone Binding Globulin
SIR	Standardized Incidence Ratio

TABLE OF CONTENTS

AGRADECIMENTOS……i

RESUMO……ii

ABSTRACT……iii

LIST OF ABBREVIATIONS……iv

INTRODUCTION……1

METHODS……3

RESULTS……4

DISCUSSION……6

Strengths and limitations……12

CONCLUSION……13

APPENDIX……14

REFERENCES……17

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a complex disorder, being the most frequent endocrinopathy among women of reproductive age. Prevalence values range from 4-21%, depending on the diagnostic criteria used and the population studied.[1] This syndrome was first described by Stein and Leventhal in 1935 in a seminal publication, in which the authors described a series of cases of women with amenorrhea and enlarged cystic ovaries, hirsutism, and infertility. [2] Until then, a relationship between enlarged ovaries and menstrual irregularities hadn't been established. Consequently, in the mid-1950s, this constellation of signs and symptoms takes on the name of Stein and Leventhal Syndrome. Later, this term was gradually abandoned and replaced by the current designation.[2] Since its first description over 80 years ago, the interest of the scientific community in this disorder has grown exponentially. This mounting interest is easily justified by the important prevalence and adverse health outcomes it is associated with.[3]

Multiple sets of criteria have been established for the diagnosis of PCOS, among which the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) criteria, more commonly known as the Rotterdam criteria, are the most widely used and accepted. According to these criteria, PCOS is defined by the presence of at least two of the following parameters: oligo-anovulation, hyperandrogenism (clinical or biochemical), and polycystic ovarian morphology. Diagnosing PCOS implicates the exclusion of other androgen excess or related disorders.[4] In 2011, the ESHRE/ASRM identified different phenotypes according to the possible combinations of present criteria. As such, it is possible to differentiate the classic phenotype, characterized by hyperandrogenism and chronic anovulation, from other phenotypes characterized by ovarian dysfunction and polycystic ovaries.[5]

In terms of clinical manifestations characterizing this syndrome, they include menstrual irregularities, amenorrhea, hirsutism and easy weight gain, usually arising in the second and third decades of life.[6] Although it might seem relatively linear to establish a PCOS diagnosis through the application of the defined criteria, PCOS is a complex and multifaceted syndrome of yet unknow etiology.[7] It is currently believed that it stems from a combination of genetic, epigenetic and environmental factors.[8]

Women diagnosed with PCOS can develop several comorbidities, namely metabolic, reproductive, cardiovascular, and oncologic.[3 9 10] The metabolic environment is characterized by reduced insulin sensitivity, peripheral insulin resistance and hyperinsulinemia. Peripheral insulin resistance is present mainly in the adipose tissue and skeletal muscle, whereas ovarian theca and granulosa cells demonstrate a high sensitivity to insulin. In the theca cells, insulin promotes the

production of androgens, namely testosterone.[11] Aromatization of androgens in the peripheral tissue perpetuates the cycle of endometrial exposure to estrogenic action, and additionally evidence suggests that androgens exert a stimulatory effect on endometrial cancer cell lines.[12]

Previous studies have demonstrated women with PCOS have higher rates of type 2 diabetes *mellitus*, independently of age and Body Mass Index (BMI).[13] Studies comprising asian and american women have shown that PCOS patients have an aproximately 5 times higher risk of developing type 2 diabetes than healthy controls.[3] This risk increases with higher waist circunference values or when excess visceral fat is present. However, even with normal BMI, some women with PCOS have metabolic disturbances due to an abnormal distribution of fat.[13] Obesity is also a very common comorbidity in these women, with Lim *et al*. reporting prevalence values of over 60%.[14 15] Therefore, it is not surprising that PCOS patients have an increased risk of developing metabolic syndrome. Metabolic syndrome is characterized by the presence of a cluster of metabolic disturbances like dyslipidaemia, hypertension, hyperglicemia and central obesity.[15] In this manner, it is easily understood that PCOS patients present a combination of classical risk factors for cardiovascular disease. There is some evidence suggesting an increased risk of premature atherosclerotic disease, and an increased risk for developing ischemic heart disease, as demonstrated by Hart and Doherty in a large Australian study.[13 16]

PCOS is considered the main cause of anovulatory infertility, however, this does not necessarily imply that all women diagnosed with PCOS are infertile. On the other hand, these patients have a higher risk of developing complications during pregnancy, such as gestational diabetes, preeclampsia, or even abortion.[9]

The unbalanced metabolic and hormonal scenario that defines PCOS can increase the risk of neoplastic disease, more specifically, hormone-related tumors such as endometrial, ovarian, or breast cancer.[17] The association between PCOS and endometrial cancer (EC) was suggested for the first time over 50 years ago.[10] Chronic anovulation, peripheral insulin resistance and hyperandrogenism constitute possible oncogenic mechanisms, particularly in the endometrium. When chronic anovulation is present, the endometrial tissue is subjected to continuous estrogenic stimulation unopposed by progesterone. Estrogens induce proliferation and differentiation in the endometrium, which can lead to hyperplasia, and ultimately to cancer.[17] Also, women with PCOS have hyperinsulinemia due to the effect of insulin resistance, which stimulates the synthesis of more insulin.[18] Besides being an important growth factor, insulin also promotes ovarian androgen production and reduces the synthesis of the sex hormone binding globulin (SHBG), contributing to an increased activity of free estrogens.[18-20] Moreover, adipose tissue cells are highly dynamic,

holding the ability to not only synthesize estrogens but also aromatize androgens into estrogens, contributing to a hyperestrogenic environment. It is currently believed that these hormonal and metabolic imbalances have a synergic role in the pathogenesis of EC.[18]

Multiple studies and international guidelines present PCOS as an established risk factor for EC. Many of the studies analyzing the risk of EC in women with PCOS do not take into account confounding factors such as obesity, a well-established risk factor for EC. Obesity is present in the majority of women with PCOS, which strongly limits the interpretation of the data obtained in said studies.[17] Thereby, the goal of the present review consists in analyzing the risk of EC in women with PCOS, accounting for the confounding factor of BMI. With this review, we intend to clarify the extent of the influence of PCOS on the risk of developing EC.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) recommendations were used to guide this review.[21]

In this systematic review, we aimed to include studies addressing the risk of EC in women with PCOS with adjustment to BMI. Meta-analyses, Systematic Reviews, Randomized Controlled Trials (RCTs) and Prospective Studies were screened. Case reports and case series were excluded from this review.

A search was conducted on PubMed, Scopus and Web of Science using the following queries: ("uterine cancer" OR "endometrial cancer") AND ("Polycystic Ovary Syndrome" OR "PCOS"). All studies identified were screened by two independent investigators for the following inclusion criteria: (1) published in English or Portuguese, (2) between January 1990 and December 2021, (3) with full-text available, (4) articles focusing on the BMI-adjusted risk of EC in women with PCOS. Two articles that met the inclusion criteria found by cross-referencing was also included.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to assess the quality of evidence of the included studies.[22] Evidence from all studies was firstly rated as “low” quality of evidence, based on the underlying methodology of observational studies. Then, studies were downgraded if there was high likelihood of bias, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, or high probability of publication bias. On the other hand, studies were upgraded if there

was a large magnitude of effect, evidence of a dose-response gradient, or all plausible confounding factors would reduce a demonstrated effect.

RESULTS

The search strategy resulted in 732 articles. Two additional articles were added by cross-referencing. In total, 391 duplicates were identified, remaining 343 articles. After examining title and abstract to determine those that met the inclusion criteria, 250 articles were excluded. The remaining 93 articles were accessed and analyzed for eligibility. Three articles weren't retrieved because the full-text version wasn't available. Of the remaining 90 articles, 85 were further excluded, for the following reasons: no relevant data about EC risk (n = 78), and no adjustment of EC risk to BMI was performed (n = 7). Five articles were finally included in this review. A PRISMA diagram of the search results is shown in Figure 1 (Appendix). The review included 3 cohort studies and 2 case-control studies. Data from the 5 five selected studies are detailed in Table I (Appendix).

Succinctly, one study [23] found a statistically significant increased risk of EC associated with PCOS after adjustment for BMI. One study found an attenuation of increased EC risk after BMI adjustment in women younger than 50 years.[24] The remaining three studies didn´t report statistically significant differences in risk after adjustment for BMI.[25-27]

Wild et al. (2000) conducted a follow-up cohort study, including 319 cohort members and 1060 controls under 75 years of age. The cohort was composed of women with: (i) confirmed PCOS diagnosis; (ii) histological evidence of polycystic ovaries (PCO) with clinical evidence not available; (iii) macroscopic evidence of PCO with clinical evidence of ovarian dysfunction and (iv) clinical evidence of ovarian dysfunction. In this paper, authors reported an increased EC risk, with an OR of 5.3 (95% confidence interval [CI] 1.5-18.6) without adjustment for BMI, and a slightly higher odds ratio (OR) of 6.1 (95% CI 1.0-36.9) after adjustment for BMI.

A case-control study conducted by Zucchetto et al. (2009) included 454 cases of women with histologically confirmed diagnosis of EC of which 25 (5.5%) women had a self-reported history of PCOS. In the control group, comprised of 908 women admitted to the same network of hospitals as the cases for unrelated causes, 43 (4.8%) women self-reported an history of PCOS. The criteria used to define PCOS were not specified in this study. The results presented were adjusted for multiple variables additionally to BMI, namely age, period of interview, age at menarche, age at menopause, parity, and OC use when appropriate. Zucchetto et al. demonstrated that overall, PCOS was not associated with EC, when accounting for BMI, reaching

an OR of 1.25 (95% CI 0.72–2.16), however, a non-significant increased risk was found in the group of premenopausal women (OR 2.03, 95% CI 0.76-5.38), based on 20 cases and 13 controls.

Fearnley et al. (2010) analyzed 156 cases of women with histologically confirmed epithelial EC and 398 age-matched controls. PCOS was defined by self-reported previous diagnosis by a doctor or signs compatible with PCOS such as hirsutism, menstrual irregularities, and acne. The authors used these signs as proxy markers for PCOS, creating a combined variable termed "PCOS-Index", that included women who self-reported any of these signs as a measure of probable undiagnosed PCOS. Before adjustment for BMI, EC risk was 4.0 (95% CI 1.7–9.3). This result was attenuated after the adjustment for BMI (OR 2.2, 95% CI 0.9–5.70). A significant positive association was also found between EC risk and the PCOS-Index variable (OR 2.1, 95% CI 1.3–3.4), however, it was also attenuated after BMI adjustment (OR 1.6, 95% CI 0.9–2.6). Fearnley et al. also explored the associations between PCOS and Type I EC, with results showing only a slight increase in risk. In the group of women with self-reported previous diagnosis of PCOS, the risk for type I EC was 4.3 (95% CI 1.8–10.2) before adjustment, and 2.4 (95% CI 1.0–6.2) after adjustment. The estimated EC risk in the PCOS-Index group was 2.2 (95% CI 1.4–3.7) before BMI adjustment, and 1.7 (95% CI 1.0–2.8) after adjustment.

Brinton et al. (2010) studied 2560 women with primary or secondary infertility who met at least one Rotterdam criteria for PCOS. Of these, 412 met the criteria for PCOS (≥2 criteria) and 2,148 met only one. Non-statistically significant excess standardized incidence ratios (SIRs) were found in the PCOS group (SIR 1.91, 95% CI 0.2-6.0), based on 2 cancers; however, the risk wasn't adjusted for BMI. This same pattern was also seen in the group of women fulfilling only one Rotterdam criteria, with results being not statistically significant (BMI non-adjusted rate ratio (RR) 1.33 [95% CI 0.69–2.58]; BMI-adjusted RR 1.17 [95% C 0.60–2.28]).

In the study conducted by Morgan et al. (2012), the population was composed of 21,734 cases of young women diagnosed with PCOS and 86,936 age-matched healthy controls within the same primary-care practice. Since the primary endpoint of this study was first incident record of diabetes, women with previous diagnosis of diabetes were excluded. Diagnostic criteria used to define PCOS were not specified. The hazard ratio (HR) for endometrial cancer was 3.990 (95% CI 1.591–10.003) before adjustment for BMI, based on 9 cases and 11 controls, and significantly decreased to 0.901 (95% CI 0.194 – 4.176) after adjustment.

DISCUSSION

The first reports suggesting an association between PCOS and EC risk were published over 70 years ago, however they were markedly limited by small sample sizes and a lack of control groups.[28] Since then, multiple systematic reviews and meta-analyses have reported a significantly higher risk of EC among PCOS patients.[29-31] In 1991, Escobedo et al. conducted a study in women with a recent diagnosis of EC, and found an increased OR for EC of 4.2 (95% CI= 1.7 – 10.4) in women with infertility associated with 'ovarian' factors.[32] In the beginning of the current century, other studies also found an increased prevalence of EC in women with PCOS, corroborating previous evidence.[33-35] Harris et al. conducted a systematic review of the literature in 2016, reporting that the majority of studies investigating the association between EC and PCOS without accounting for BMI reach statistically significant increased EC risk values for women with PCOS.[10] The most recent meta-analysis, that focuses on the risk of EC in women with PCOS reports an overall increased risk of EC of 2.79 (95% CI 1.31–5.95) without BMI-adjustment.[31]

The 2018 guidelines issued by ESHRE/ASRM recognize the extensively studied relationship between PCOS and EC, advising endometrial surveillance by transvaginal ultrasound or endometrial biopsy in PCOS patients who have thickened endometrium, prolonged amenorrhea, unopposed estrogen exposure or abnormal vaginal bleeding, based upon clinical suspicion.[36] Nonetheless, the studies included in these guidelines don't consider the possible confounding effects of obesity.[10 31] In the current state of knowledge, obesity is considered a well-established, independent risk factor for EC with the risk increasing up to 60% for every 5-unit increase in BMI. [37 38] Furthermore, obesity is a highly prevalent characteristic in women with PCOS.[14] Evidence suggests that the great majority of women seeking treatment for PCOS have excess weight, and a higher genetic susceptibility to obesity also seems to be present in these women.[39 40] A systematic review conducted by Lim et al. in 2012, reported an estimated pooled prevalence of obesity of 61% in women with PCOS.[14] Likewise, evidence also suggests that weight control is beneficial for improving PCOS symptoms and decreasing endometrial thickness, indicating its possibly crucial role in diminishing EC risk in PCOS women.[41] With this systematic review, we intended to evaluate the relationship between PCOS and EC when adjustment of results to BMI was performed, with the intention of understanding the exact role of PCOS in EC development.

Although OR values vary between studies, our findings indicate that the contribution of PCOS to the increased EC risk is smaller than previous literature has suggested. Only Wild et al.'s results indicate the contrary, with BMI adjustment increasing this risk. [23] Fearnley et al. reported a decrease in risk after BMI-adjustment, demonstrating a significantly increased risk for type I EC.[24]

Brinton et al. reported a non-statistically significant increased EC risk among infertile women fulfilling at least one Rotterdam criteria.[26] Zucchetto et al. presented similar results, reporting no increase EC risk in PCOS women; however, in this case the authors solely reported values after BMI adjustment, which renders it difficult to draw illations from the unadjusted results, which were not included in the article.[27] Morgan et al. also found no increased risk after adjustment for BMI.[25]

Heterogeneity in EC risk and conclusions between studies may be partially due to differences in PCOS definition, selected populations, and adjustment for confounders between the analyzed studies. Zuchetto et al. adjusted results for parity, OC use, age at menarche and age at menopause and Fearnley et al. adjusted for age, parity, oral contraceptive use and type II diabetes. The remaining authors adjusted only to BMI. The discrepancies in PCOS definition between studies pose as an important limiting factor in the comparison and interpretation of results, as there are inconsistencies in the definition of cases. Although PCOS was first described in 1935, guidance on establishing a diagnosis only emerged in 1990.[2 29] Since then, other sets of criteria that expanded the definition of PCOS were created and started including the presence of polycystic ovarian morphology alongside hyperandrogenism and oligo-anovulation. The flexibility of the criteria allows for a wide spectrum of patients to be categorized as having PCOS.[29] This broad definition raises the question of whether all women with a PCOS diagnosis suffer the same long-term health consequences.[42] Whilst Wild et al. and Brinton et al. used clear criteria to define PCOS, the other authors failed to specify objective criteria or relied on self-reported diagnosis/symptoms of PCOS by the included women.[23 26] Wild et al. relied on histological confirmation of polycystic ovarian morphology and clinical evidence of chronic anovulation (oligomenorrhea or amenorrhea), and androgen excess (hirsutism) to assess PCOS presence. [23] Brinton et al. used the Rotterdam criteria, the currently most widely used and accepted set of criteria to define PCOS.[26] Zucchetto et al. and Fearnley et al. included women with self-reported PCOS diagnosis, which can lead to recall bias and inclusion of women without criteria for PCOS diagnosis.[24 27] Fearnley et al. also included women reporting PCOS symptoms such as hirsutism, severe acne or menstrual irregularities. Although at first glance this approach seems faulty since it could lead to inclusion of women without PCOS, the authors classified these symptoms as proxy-markers for undiagnosed PCOS, analyzing these women separately. A possible source of limitation to this study were the varying methods for information collection, since in the first wave of controls the questionnaire was self-administered, and in the second wave the questionnaire was administered by telephone interview both to cases and controls.[24] Morgan et al. relied on medical records to assess PCOS diagnosis, however there was no information related to the

clinical or biochemical criteria by which the PCOS was established. This approach poses as a limitation to this study since authors were unable to confirm a correct attribution of the diagnosis.[25] Although Brinton et al. used clear criteria to select patients, the subset of patients for which BMI adjusted EC risk values are included comprises patients meeting at least one Rotterdam criteria. This means the risk estimate includes women who do not fulfill the criteria for PCOS diagnosis, hampering any definite conclusion.[26]

This review is also affected by the selection of varying case patient's characteristics. For example, Fearnley at al. and Zucchetto et al. selected women with a diagnosis of EC, while Brinton et al. selected cases from a pool of patients who had sought healthcare providers' advice for primary or secondary infertility, possibly including women with varying severity of PCOS phenotype.[24 26 27] PCOS itself is a heterogeneous syndrome that comprises varying degrees of phenotype severity. This can contribute to the heterogeneity of results since some phenotypes may face a higher risk of EC than others.

EC is classically divided into two subtypes: type I, the most prevalent and estrogen-dependent in nature, and type II, which is more aggressive and thought to be estrogen-independent. PCOS associated chronic oligo-anovulation, hyperandrogenism, hyperinsulinemia and genetic predisposition are believed to be involved in EC etiopathology. Specifically, it is thought that PCOS is mainly associated with type I EC, which is generally attributed to long-term exposure to estrogen unopposed by progesterone and is mostly correlated with obesity and other frequent comorbidities associated with the syndrome. PCOS women also differ from the general female population. In the latter, EC is commonly diagnosed in postmenopausal women with a mean age of 70 years, whereas premenopausal women with PCOS seem to face a higher risk, as will be discussed further on.[43]

The transition from reproductive age to menopause represents a period of important changes and brings along its own long-term health risks. A longitudinal study with a 20 year follow-up period confirmed that the PCOS phenotype ameliorates with aging, and some patients no longer fulfill the diagnosis criteria by the fourth decade of life.[44] Nevertheless, it is unclear whether this improvement in phenotype correlates to a reduction in health risks associated with PCOS, including EC.[1] In the most recent systematic review and meta-analysis on EC risk in women with PCOS, OR values increased significantly when analysis was restricted to women under 54 years of age. Included studies were however hampered by a lack of control for confounders, small number of cases and self-reported PCOS diagnosis.[31] A recent Danish cohort study with more than 12,000 subjects with PCOS also corroborated these results. In this paper, the authors showed

that EC risk decreased to half and was no longer statistically significant when only women over 50 years were considered.[45] Fearnley et al. findings pertain to the analysis of premenopausal women (<50 years), with results suggesting an overall increased EC risk in this population.[24] Although Zucchetto et al.'s findings suggest that EC risk is not increased in PCOS women, when analyzing only the subset of premenopausal patients, an non-statistically significant increased risk was found (OR = 2.03 95% CI = 0.76–5.38).[27] In the remaining studies included in this systematic review, a sub-analysis of the risk before and after menopause was not performed. Of notice that these values relate to a very reduced number of cases. Current evidence suggests that the risk of EC in women with PCOS may be attenuated after menopause, however it is yet insufficient and further studies are necessary to assess this effect. It is crucial to remember that an endometrial cancer diagnosis can have important implications in the quality of life of these young patients, namely fertility implications. A recent retrospective chart review analyzed 69 women with endometrial hyperplasia, EC or that had been subjected to endometrial sampling, aiming at identifying risk factors that might warrant endometrial sampling before 25 years of age. The authors found obesity to be associated with an increased risk of EC, however PCOS alone was not identified as a risk factor for EC or hyperplasia.[46] These findings put forth the possibility that the increased EC risk attributed to women with PCOS might be due to long-term exposure to the endocrine and metabolic alterations that characterize the syndrome, or due to a conjugation of other factors.

Other factors commonly found in women with PCOS, such as type 2 diabetes and metabolic syndrome have also been associated with cancer risk and thus, act as possible confounders of the PCOS-cancer association.[47 48] A large meta-analysis involving 7596 cases of EC reported a significant association between diabetes and EC risk with a RR of 2.10 (95% CI 1.75–2.53).[49] Another large systematic-review and meta-analysis including 25 studies reported a strong association between hypertension and EC, suggesting that women with an hypertension diagnosis may face a 61% increase in the relative risk of developing endometrial cancer.[50]

In terms of clinical prognosis, in a recent retrospective cohort study, Uehara et al. found that PCOS women show a higher rate of EC recurrence after surgery than patients without PCOS. Authors suggested that insulin resistance (IR) and its related endocrine milieu are associated with recurrence, raising the question of whether IR targeting therapy such as metformin might be useful to stop EC progression.[51] Although mechanisms of carcinogenesis are not fully understood, with regards to the EC risk in PCOS, IR and consequent hyperinsulinemia seem to play important roles.[52] The most accepted hypothesis is based on the mitogenic effect insulin exerts through the

insulin-like growth factor-1 (IGF-1) receptor and the oxidative stress caused by hyperglycemia.[53] Metformin prescription to PCOS patients has increased in the context of infertility, obesity, and hirsutism but not as a measure to prevent EC, however it has been shown that metformin has an antiproliferative effect on multiple cancers.[52 54] In vitro studies have shown that metformin inhibits the growth of endometrial cancer cells and attenuates their invasive and metastatic power.[53] Still, a large case-control analysis exploring the relationship between the use of metformin and the risk of EC determined that there were no differences in cancer incidences between the patients who had never used metformin and those who had.[55] Similarly, a retrospective cohort study that compared the incidence of EC in metformin versus sulfonylurea initiators (non-PCOS patients), determined that metformin did not correlate to a decrease in risk of developing EC when compared to sulfonylureas.[56] Currently, the research supporting the use of metformin in women with PCOS with the goal to prevent EC is still scarce and more evidence on this topic is needed.[52]

Considering EC prevention in women diagnosed with PCOS, the use of oral contraceptives (OC) may play a role in these patients, since the endometrial tissue of women with PCOS is subjected to the continuous effect of unopposed estrogens. OC's are associated with decreased risk of EC once they limit the exposure of endometrial cells to unopposed estrogen, thus reducing cell proliferation.[10] A high quality pooled analyses encompassing 36 epidemiological studies also showed that the more prolonged the use of OC's is, the greater the reduction in risk.[57] Supporting this evidence, a large retrospective study showed a reduction of 33% in incidence of EC, with protective effects lasting for over 30 years.[58]

It is important to recognize features of PCOS unrelated to obesity that may be implicated in EC pathogenesis. The action of unopposed estrogens is considered the main mechanism implicated in endometrial carcinogenesis. Due to the oligo-anovulation that characterizes PCOS, the endometrium is exposed to continuous mitogenic estrogen activity unbalanced by the inhibitory effects of progesterone, and a chronic progesterone-deficient state ensues.[43 59] Current evidence also suggests women with PCOS demonstrate endometrial progesterone resistance, with progesterone effects diminished even in the presence of ovulation and treatment with exogenous progestin.[43 60] The estrogen-driven proliferation may induce endometrial hyperplasia and ultimately lead to the development of a neoplastic disorder.[17]

Alongside the unopposed estrogen action in endometrial tissue, hyperandrogenism has also been proposed as a causal factor for the increased EC risk in women with PCOS. Androgens exert their effects directly through androgen receptors (AR), which have shown to have an

increased endometrial expression in women with PCOS, but also indirectly as precursors for local estrogen synthesis.[61] [62] Also, a correlation between hyperplasia and an over-expression of AR has been reported in women with PCOS.[59] Adding to this, epidemiological data reveal that EC risk in postmenopausal women correlates to elevated levels of total and free testosterone. However, the same correlation was not found in premenopausal women, with analyses suggesting that peripheral conversion of androgens into estradiol could represent a more impactful causal factor for an increased EC risk in this age group.[63] A recent study conducted by Wiwapanit et al. set out to evaluate the effects of increased androgens levels seen in PCOS in scaffold-free endometrial organoids. The authors concluded that administration of PCOS hormones dysregulated genes as well as increased cell proliferation in the specimens. In the light of these findings, chronically increased androgen levels would promote cell proliferation and consequent accumulation of mutations, and loss of differentiation, eventually progressing to neoplastic transformation.[64] Nonetheless, studies in this field have reported conflicting evidence when it comes to role of androgens in the endometrium, with studies attributing both a proliferative and anti-proliferative role to androgens.[61] The possible impact of androgens in endometrial cancer is not yet clarified and further investigation in this field is necessary.

To improve insulin resistance, which seems to be closely related to EC pathogenesis, the establishment of a low-glycemic index (GI) diet has been suggested by several authors, as it is plausible that it could reduce the risk of EC.[41] [65] In line with this, Silvera et al.'s findings suggest that a high dietary glycemic load may correlate with increased risk of EC overall.[66] The implementation of a low-GI diet may have short and long-term implications, improving the symptoms in the present and reducing the risk of comorbidities related to IR in the future.[67] Further research into measures to attenuate EC risk in high-risk women is crucial to decrease morbidity and mortality in these populations.

Other mechanisms such as inflammation and oxidative stress (OS) have also been suggested as contributing for the neoplastic potential observed in women with PCOS. Despite the multifaceted character of PCOS, OS and low-grade inflammation seem to a be a constant presence, independently of BMI.[68] Inflammation is implicated in the pathogenesis of multiple chronic pathologies, and PCOS is no exception. Increased levels of markers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor α (TNF-α) and interleukin-8 (IL-8), among others have been reported in women with PCOS.[69] A chronic inflammatory state can accelerate the rate of cell division, therefore increasing the chance of replication errors, DNA damage and consequent mutations occurring.[70] In a recent review, Zhang et al. reported that PCOS patients

also exhibit mitochondrial dysfunction, a factor that has been shown to be vital in cardiovascular disease, type 2 Diabetes *mellitus* and cancer.[69]

As a complex and multidimensional syndrome, the pathogenesis of PCOS is yet to be fully understood. The interest of investigators on phosphatidylinositol 3-kinase (PI3K) has been increasing, since it has been recognized that it plays an important role in PCOS. Research has shown that the PI3K-protein kinase B (Akt) signaling pathway has significant effects on insulin resistance and EC. This signaling pathway has also been implied in processes such as inflammation, cell proliferation and apoptosis, and plays an important role in the occurrence of multiple neoplastic disorders in the lung, bladder and bone.[71] While studying cell cycle regulators, Villavicencio et al. found an excessive phosphorylation of the downstream target protein Akt in endometrial cells in women with PCOS. This phenomenon dysregulated the cell cycle and endometrial atypical hyperplasia/carcinoma ensued.[72] Complex molecular interactions are most likely responsible for the increased risk of EC in women with PCOS, and further research and understanding of this relationship is crucial to prevent adverse health outcomes and to decrease mortality in PCOS patients.

Overall, our findings suggest that EC risk appears to be only slightly increased or equal to the general population when we account for the BMI. This is an important finding since successful weight control in these patients probably reduces substantially their risk of developing EC, lowering it to values similar to those of women without the syndrome. Other confounding factors can interfere with these results, such as nulliparity, hypertension, type II diabetes and metabolic syndrome, all of which are more frequent among women with PCOS. The risk also seems to vary according to menopausal status, although the evidence is insufficient to draw definitive conclusions.

Strengths and limitations

Possible limitations to this review include publication bias since it only considered studies in English and Portuguese. There is also a lack of strong evidence for the included studies (very low to low quality evidence, n = 5 studies), mainly derived from the methodological types of studies included (only observational studies met the inclusion criteria) which is an important limiting factor. Additionally, the heterogeneity of results found illustrates the differences between studies in establishment of PCOS definition, and therefore renders it difficult to compare and equate results. Also, due to the inclusion of self-reported symptoms/PCOS diagnosis, the presented EC risk values possibly include women without PCOS.

The strengths of the current review include the application of the GRADE methodology to evaluate the quality of evidence. This systematic review provides an important insight into the relationship between PCOS and EC and contributes to raise awareness about the necessity to perform BMI-adjustment when evaluating EC risk in this specific population. This knowledge adds to an increased accuracy in future studies that investigate this intricate relationship. Additionally, these results help shift the current perspective about the role of PCOS alone in the increased EC risk attributed to these women, suggesting that it's contribution could be significantly less important than expected. In this sense, there is still a long way to go in the discovery and understanding of the mechanisms that connect PCOS and EC.

CONCLUSION

EC risk in women with PCOS appears to be equal or slightly increased to the EC risk of non-PCOS women when adjustment for BMI is performed, however the heterogeneity in our findings don't allow for a solid conclusion to be drawn. Nonetheless, there appears to exist a benefit in weight-control in PCOS patients in order to not only decrease EC risk, but also to prevent comorbidities associated with obesity, such as hypertension and diabetes, that also contribute to EC risk.

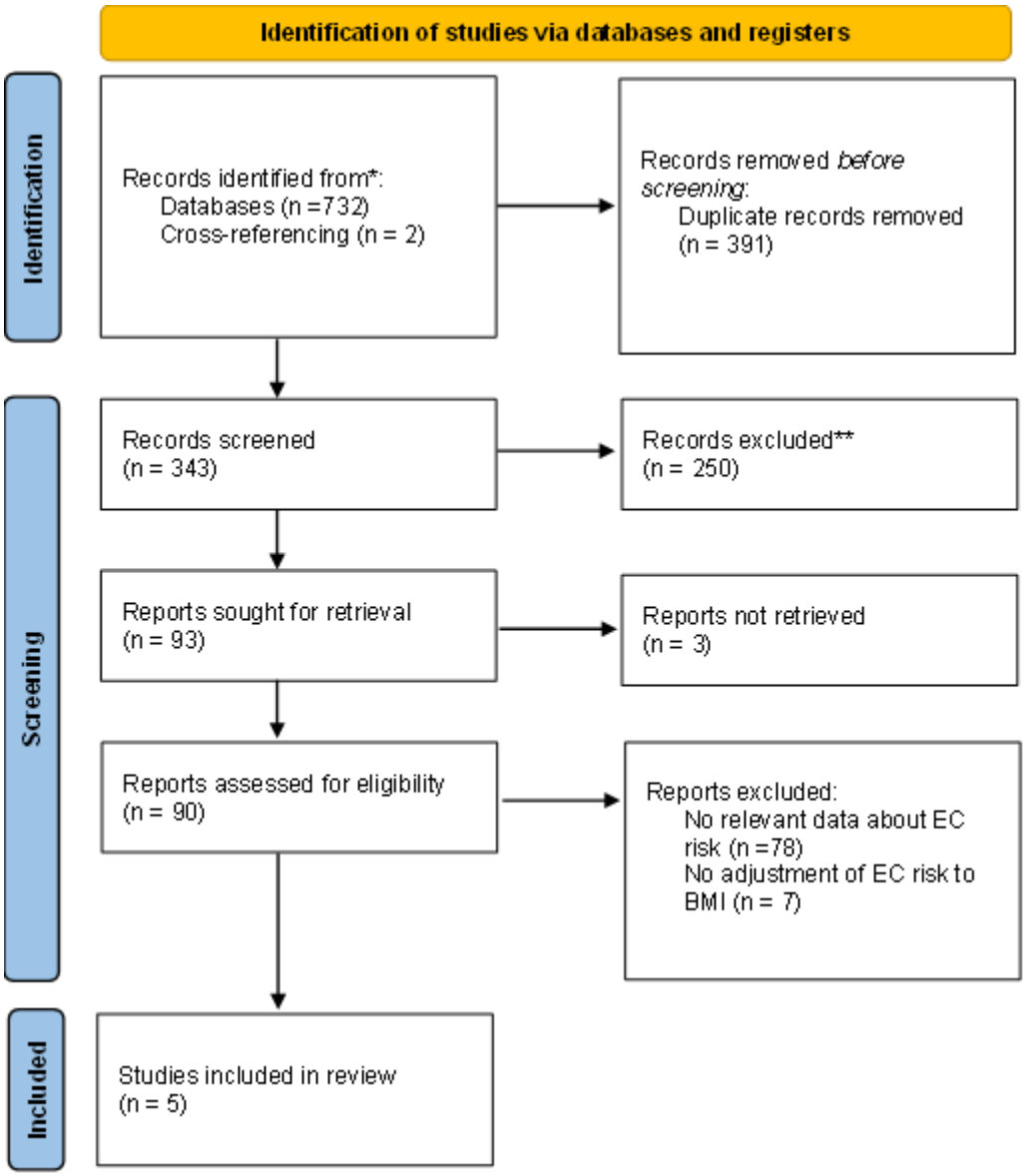

Figure 1. Flow-chart of the literature research (PRISMA-P)

Table I. Summary of evidence

Author	Country; Year of publication	Study Design	PCOS definition/diagnosis	Population	Results	Conclusion	Level of evidence
Wild, S. *et al*	UK, 2000	Follow-up cohort study	Confirmed PCOS diagnosis (histological evidence of PCO with clinical evidence of ovarian dysfunction) OR histological evidence of PCO with clinical evidence not available OR macroscopic evidence of PCO with clinical evidence of ovarian dysfunction OR clinical diagnosis[a]	N= 1379 (319 cohort members and 1060 controls) Women with a previous diagnosis of PCOS	EC risk BMI non-adjusted OR 5.3, 95% CI 1.5-18.6 EC risk BMI adjusted OR 6.1, 95% CI 1.0-36.9 (P= 0.05)	Women with PCOS are at higher risk of EC and this relationship cannot be explained by confounding by obesity.	Low
Zucchetto, A. *et al*	Italy, 2009	Case-control study	Self-reported PCOS diagnosis[b]	N=1362 454 cases (women with histologically confirmed diagnosis of endometrial cancer one year before enrollment and no earlier diagnosis of cancer) 908 controls (women admitted without gynecological or hormone-related conditions and without prior history of hysterectomy)	EC risk BMI-adjusted OR 1.25, 95% CI 0.72–2.16[c] **Pre-menopausal women**: EC risk BMI-adjusted OR 2.03, 95% CI 0.76–5.38	PCOS did not increase the risk of EC when adjusted for BMI, although there was a non-significant increased risk among premenopausal women with PCOS.	Very low
Brinton, L. *et al*	USA, 2010	Retrospective cohort study	PCOS defined by ≥2 Rotterdam criteria Women fulfilling at least one Rotterdam criteria were also included to expand the cohort[d]	N=2560 Women with primary or secondary infertility who met at least one Rotterdam criteria for PCOS.	**≥2 Rotterdam criteria:** EC risk BMI non-adjusted SIR 1.91, 95% CI 0.2-6.0 **≥1 Rotterdam criteria** EC risk BMI non-adjusted RR 1.33; 95% CI 0.69–2.58 EC risk BMI-adjusted RR 1.17; 95% C 0.60–2.28	Among women with infertility, those with at least one Rotterdam criteria (androgen excess or menstrual disorder) have a statistically non-significant increased risk of developing EC; this risk is further attenuated after adjustment to BMI	Very low
Fearnley, E. *et al*	Australia, 2010	Case-control study	Self-reported previous diagnosis of PCOS by a doctor OR symptoms compatible with PCOS[b]	N= 554 156 cases (women <50y old at diagnosis of a histologically confirmed epithelial endometrial cancer) 398 controls	**PCOS:** EC risk BMI non-adjusted OR 4.0, 95% CI 1.7–9.3 EC risk BMI adjusted OR 2.2, 95% CI 0.9–5.7 **Type I EC cases:**	PCOS increases the risk of EC in women younger than 50, although to a lesser extent after BMI adjustment and this relationship is stronger if limited to type I	Very low

				(age-matched women without prior hysterectomy or endometrial cancer)	EC risk BMI non-adjusted OR 4.3, 95% CI 1.8–10.2 EC risk BMI adjusted OR 2.4, 95% CI 1.0–6.2 **PCOS-Index[e]:** EC risk BMI non-adjusted OR 2.1, 95% CI 1.3–3.4 EC risk BMI adjusted OR 1.6, 95% CI 0.9–2.6 **PCOS-Index Type I EC cases:** EC risk BMI non-adjusted OR 2.2, 95% CI 1.4–3.7 EC risk BMI adjusted OR 1.7, 95% CI 1.0–2.8	cancers.	
Morgan, C. *et al*.	UK, 2012	Retrospective cohort study	Previous PCOS diagnosis[b]	N=108,670 21,734 cases (women diagnosed with PCOS between 1990 and 2010) 86,936 controls (age-matched healthy women within the same primary-care practice)	EC risk BMI non-adjusted HR 3.990, 95% CI 1.591–10.003 EC risk BMI-adjusted HR 0.901, 95% CI 0.194 – 4.176	PCOS increased EC risk, although adjustment for BMI significantly attenuated this association to a nonsignificant difference from controls.	Very low

a. Clinical evidence of chronic anovulation (oligomenorrhea or amenorrhea), and androgen excess (hirsutism).

b. Diagnosis criteria not specified.

c. Results presented were adjusted for age, period of interview, age at menarche, age at menopause, parity, and OC use when appropriate.

d. Data collected through clinical registries.

e. Women who self-reported any symptoms of PCOS such as acne, hirsutism, or very irregular periods as a possible measure of any undiagnosed PCOS.

REFERENCES

1. Helvaci N, Yildiz BO. *Polycystic ovary syndrome and aging: Health implications after menopause*. Maturitas. 2020;139:12-19.
2. Azziz R, Adashi EY. *Stein and Leventhal: 80 years on*. Am J Obstet Gynecol. 2015;214(2):247.e1-47.e11.
3. Allen LA, Shrikrishnapalasuriyar N, Rees DA. *Long-term health outcomes in young women with polycystic ovary syndrome: A narrative review*. Clin Endocrinol (Oxf). 2021
4. Azziz R, Carmina E, Dewailly D, et al. *The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report*. Fertil Steril. 2009;91(2):456-88.
5. Palomba S, Santagni S, Falbo A, et al. *Complications and challenges associated with polycystic ovary syndrome: current perspectives*. Int J Womens Health. 2015;7:745-63.
6. Meczekalski B, Pérez-Roncero GR, López-Baena MT, et al. *The polycystic ovary syndrome and gynecological cancer risk*. Gynecol Endocrinol. 2020;36(4):289-93.
7. Rodriguez Paris V, Bertoldo MJ. *The Mechanism of Androgen Actions in PCOS Etiology*. Med Sci (Basel). 2019;7(9):89.
8. Faghfoori Z, Fazelian S, Shadnoush M, et al. *Nutritional management in women with polycystic ovary syndrome: A review study*. Diabetes Metab Syndr. 2017;11 Suppl 1:S429-s32.
9. Gilbert EW, Tay CT, Hiam DS, et al. *Comorbidities and complications of polycystic ovary syndrome: An overview of systematic reviews*. Clin Endocrinol (Oxf). 2018;89(6):683-99.
10. Harris HR, Terry KL. *Polycystic ovary syndrome and risk of endometrial, ovarian, and breast cancer: a systematic review*. Fertil Res Pract. 2016;2:14.
11. Lauretta R, Lanzolla G, Vici P, et al. *Insulin-Sensitizers, Polycystic Ovary Syndrome and Gynaecological Cancer Risk*. Int J Endocrinol. 2016;2016:8671762.
12. Navaratnarajah R, Pillay OC, Hardiman P. *Polycystic ovary syndrome and endometrial cancer*. Semin Reprod Med. 2008;26(1):62-71.
13. Ali AT, Guidozzi F. *Midlife women's health consequences associated with polycystic ovary syndrome*. Climacteric. 2020;23(2):116-22.
14. Lim SS, Davies MJ, Norman RJ, et al. *Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis*. Hum Reprod Update. 2012;18(6):618-37.
15. Cooney LG, Dokras A. *Beyond fertility: polycystic ovary syndrome and long-term health*. Fertil Steril. 2018;110(5):794-809.
16. Hart R, Doherty DA. *The Potential Implications of a PCOS Diagnosis on a Woman's Long-Term Health Using Data Linkage*. J Clin Endocrinol Metab. 2015;100(3):911-19.
17. Ignatov A, Ortmann O. *Endocrine Risk Factors of Endometrial Cancer: Polycystic Ovary Syndrome, Oral Contraceptives, Infertility, Tamoxifen*. Cancers (Basel). 2020;12(7)
18. Li X, Shao R. *PCOS and obesity: insulin resistance might be a common etiology for the development of type I endometrial carcinoma*. Am J Cancer Res. 2014;4(1):73-9.
19. Ding DC, Chen W, Wang JH, et al. *Association between polycystic ovarian syndrome and endometrial, ovarian, and breast cancer: A population-based cohort study in Taiwan*. Medicine (Baltimore). 2018;97(39):e12608.
20. Glintborg D, Andersen M. *Medical comorbidity in polycystic ovary syndrome with special focus on cardiometabolic, autoimmune, hepatic and cancer diseases: an updated review*. Curr Opin Obstet Gynecol. 2017;29(6):390-96.
21. Moher D, Shamseer L, Clarke M, et al. *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement*. Systematic Reviews. 2015;4(1):1.
22. Schünemann H BJ, Guyatt G, Oxman A, editors. *GRADE handbook for grading quality of evidence and strength of recommendations*. The GRADE Working Group. 2013
23. Wild S, Pierpoint T, Jacobs H, et al. *Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study*. Hum Fertil (Camb). 2000;3(2):101-05.
24. Fearnley EJ, Marquart L, Spurdle AB, et al. *Polycystic ovary syndrome increases the risk of endometrial cancer in women aged less than 50 years: an Australian case-control study*. Cancer Causes Control. 2010;21(12):2303-8.
25. Morgan CL, Jenkins-Jones S, Currie CJ, et al. *Evaluation of Adverse Outcome in Young Women with Polycystic Ovary Syndrome Versus Matched, Reference Controls: A Retrospective, Observational Study*. J Clin Endocrinol Metab. 2012;97(9):3251-60.
26. Brinton LA, Moghissi KS, Westhoff CL, et al. *Cancer risk among infertile women with androgen excess or menstrual disorders (including polycystic ovary syndrome)*. Fertil Steril. 2010;94(5):1787-92.
27. Zucchetto AS, Diegoa; Polesel, Jerrya; Negri, Evab; De Paoli, Angelaa; Dal Maso, Luiginoa; Montella, Mauriziod; La Vecchia, Carlob c; Franceschi, Silviae; Talamini, Renatoa. *Hormone-related factors and gynecological conditions in relation to endometrial cancer risk*. Eur J Cancer Prev. 2009;18(4):316-21.
28. Hardiman P, Pillay OC, Atiomo W. *Polycystic ovary syndrome and endometrial carcinoma*. Lancet. 2003;361(9371):1810-2.
29. Chittenden BG, Fullerton G, Maheshwari A, et al. *Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review*. Reprod Biomed Online. 2009;19(3):398-405.
30. Haoula Z, Salman M, Atiomo W. *Evaluating the association between endometrial cancer and polycystic ovary syndrome*. Hum Reprod. 2012;27(5):1327-31.

31. Barry JA, Azizia MM, Hardiman PJ. *Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis*. Hum Reprod Update. 2014;20(5):748-58.
32. Escobedo LG, Lee N, C., Peterson HBW, P.A. . *Infertility-associated endometrial cancer risk may be limited to specific subgroups of infertile women*. Obstet Gynecol. 1991;77(1):124-28.
33. Niwa K, Imai A, Hashimoto M, et al. *A case-control study of uterine endometrial cancer of pre- and post-menopausal women*. Oncol Rep. 2000;7(1):89-93.
34. Pillay OC, Te Fong LF, Crow JC, et al. *The association between polycystic ovaries and endometrial cancer*. Hum Reprod. 2006;21(4):924-9.
35. Iatrakis G, Zervoudis S, Saviolakis A, et al. *Women younger than 50 years with endometrial cancer*. Eur J Gynaecol Oncol. 2006;27(4):399-400.
36. Teede HJ, Misso ML, Costello MF, et al. *Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome*. Hum Reprod. 2018;33(9):1602-18.
37. Clinton SK, Giovannucci EL, Hursting SD. *The World Cancer Research Fund/American Institute for Cancer Research Third Expert Report on Diet, Nutrition, Physical Activity, and Cancer: Impact and Future Directions*. J Nutr. 2020;150(4):663-71.
38. Webb PM. Obesity and Gynecologic Cancer Etiology and Survival: American Society of Clinical Oncology (ASCO) 2013.
39. Moran LJ, Brinkworth G, Noakes M, et al. *Effects of lifestyle modification in polycystic ovarian syndrome*. Reprod Biomed Online. 2006;12(5):569-78.
40. Day FR, Hinds DA, Tung JY, et al. *Causal mechanisms and balancing selection inferred from genetic associations with polycystic ovary syndrome*. Nat Commun. 2015;6:8464.
41. Atiomo W, Read A, Golding M, et al. *Local recruitment experience in a study comparing the effectiveness of a low glycaemic index diet with a low calorie healthy eating approach at achieving weight loss and reducing the risk of endometrial cancer in women with polycystic ovary syndrome (PCOS)*. Contemp Clin Trials. 2009;30(5):451-6.
42. Broekmans FJ, Knauff EA, Valkenburg O, et al. *PCOS according to the Rotterdam consensus criteria: Change in prevalence among WHO-II anovulation and association with metabolic factors*. Bjog. 2006;113(10):1210-7.
43. Piltonen TT. *Polycystic ovary syndrome: Endometrial markers*. Best Pract Res Clin Obstet Gynaecol. 2016;37:66-79.
44. Carmina E, Campagna AML, R.A. *A 20-year follow-up of young women with polycystic ovary syndrome*. Obstet Gynecol. 2012;119(2 Part 1):263-9.
45. Gottschau M, Kjaer SK, Jensen A, et al. *Risk of cancer among women with polycystic ovary syndrome: a Danish cohort study*. Gynecol Oncol. 2015;136(1):99-103.
46. Rosen MW, Tasset J, Kobernik EK, et al. *Risk Factors for Endometrial Cancer or Hyperplasia in Adolescents and Women 25 Years Old or Younger*. J Pediatr Adolesc Gynecol. 2019;32(5):546-49.
47. Shikata K, Ninomiya T, Kiyohara Y. *Diabetes mellitus and cancer risk: review of the epidemiological evidence*. Cancer Sci. 2013;104(1):9-14.
48. Giovannucci E. *Metabolic syndrome, hyperinsulinemia, and colon cancer: a review*. Am J Clin Nutr. 2007;86(3):s836-42.
49. Friberg E, Orsini N, Mantzoros CS, et al. *Diabetes mellitus and risk of endometrial cancer: a meta-analysis*. Diabetologia. 2007;50(7):1365-74.
50. Aune D, Sen A, Vatten LJ. *Hypertension and the risk of endometrial cancer: a systematic review and meta-analysis of case-control and cohort studies*. Sci Rep. 2017;7:44808.
51. Uehara T, Mitsuhashi A, Shozu M. *The impact of pre-existing polycystic ovary syndrome on endometrial cancer recurrence*. Eur J Gynaecol Oncol. 2020;41(5):668-74.
52. Shafiee MN, Khan G, Ariffin R, et al. *Preventing endometrial cancer risk in polycystic ovarian syndrome (PCOS) women: could metformin help?* Gynecol Oncol. 2014;132(1):248-53.
53. Imai A, Ichigo S, Matsunami K, et al. *Clinical benefits of metformin in gynecologic oncology (Review)*. Oncology Letters. 2015;10(2):577-82.
54. Dowling RJO, Goodwin PJ, Stambolic V. *Understanding the benefit of metformin use in cancer treatment*. BMC Medicine. 2011;9(1):33.
55. Becker C, Jick SS, Meier CR, et al. *Metformin and the risk of endometrial cancer: a case-control analysis*. Gynecol Oncol. 2013;129(3):565-9.
56. Ko EM, Sturmer T, Hong JL, et al. *Metformin and the risk of endometrial cancer: A population-based cohort study*. Gynecol Oncol. 2015;136(2):341-47.
57. Collaborative Group on Epidemiological Studies on Endometrial Cancer. *Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies*. Lancet Oncol. 2015;16(9):1061-70.
58. Iversen L, Sivasubramaniam S, Lee AJ, et al. *Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study*. Am J Obstet Gynecol. 2017;216(6):580 e1-80 e9.
59. Villavicencio A, Bacallao K, Avellaira C, et al. *Androgen and estrogen receptors and co-regulators levels in endometria from patients with polycystic ovarian syndrome with and without endometrial hyperplasia*. Gynecol Oncol. 2006;103(1):307-14.
60. Li X, Feng Y, Lin J-F, et al. *Endometrial progesterone resistance and PCOS*. J Biomed Sci. 2014;21(1):2-2.

61. Bianchi VE, Bresciani E, Meanti R, et al. *The role of androgens in women's health and wellbeing*. Pharmacol Res. 2021;171
62. Apparao KB, Lovely LP, Gui Y, et al. *Elevated endometrial androgen receptor expression in women with polycystic ovarian syndrome*. Biol Reprod. 2002;66(2):297-304.
63. Allen NE, Key TJ, Dossus L, 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(2):485-97.
64. Wiwatpanit T, Murphy AR, Lu Z, et al. *Scaffold-Free Endometrial Organoids Respond to Excess Androgens Associated With Polycystic Ovarian Syndrome*. J Clin Endocrinol Metab. 2020;105(3):769-80.
65. Herriot AM, Whitcroft S, Jeanes Y. *An retrospective audit of patients with polycystic ovary syndrome: the effects of a reduced glycaemic load diet*. J Hum Nutr Diet. 2008;21(4):337-45.
66. Silvera SA, Rohan TE, Jain M, et al. *Glycaemic index, glycaemic load and risk of endometrial cancer: a prospective cohort study*. Public Health Nutr. 2005;8(7):912-9.
67. Marsh K, Brand-Miller J. *The optimal diet for women with polycystic ovary syndrome?* Br J Nutr. 2005;94(2):154-65.
68. Mancini A, Bruno C, Vergani E, et al. *Oxidative Stress and Low-Grade Inflammation in Polycystic Ovary Syndrome: Controversies and New Insights*. Int J Mol Sci. 2021;22(4):1667.
69. Zhang J, Bao Y, Zhou X, et al. *Polycystic ovary syndrome and mitochondrial dysfunction*. Reprod Biol Endocrinol. 2019;17(1):67.
70. Modugno F, Ness RB, Chen C, et al. *Inflammation and endometrial cancer: a hypothesis*. Cancer Epidemiol Biomarkers Prev. 2005;14(12):2840-7.
71. Li T, Mo H, Chen W, et al. *Role of the PI3K-Akt Signaling Pathway in the Pathogenesis of Polycystic Ovary Syndrome*. Reprod Sci. 2017;24(5):646-55.
72. Villavicencio A, Goyeneche A, Telleria C, et al. *Involvement of Akt, Ras and cell cycle regulators in the potential development of endometrial hyperplasia in women with polycystic ovarian syndrome*. Gynecol Oncol. 2009;115(1):102-07.