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Item Type	info:eu-repo/semantics/article
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Citation	: Hernandez AV, et al., Insulin resistance and endometrial cancer risk: A systematic review and meta-analysis, European Journal of Cancer (2015), http://dx.doi.org/10.1016/j.ejca.2015.08.031
DOI	10.1016/j.ejca.2015.08.031
Publisher	Elsevier B.V.
Journal	European Journal of Cancer
Rights	info:eu-repo/semantics/openAccess
Download date	02/09/2022 13:46:08
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ARTICLE *in* EUROPEAN JOURNAL OF CANCER · DECEMBER 2015

Impact Factor: 5.42 · DOI: 10.1016/j.ejca.2015.08.031

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Review

Insulin resistance and endometrial cancer risk: A systematic review and meta-analysis

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Received 22 June 2015; received in revised form 24 August 2015; accepted 30 August 2015

KEYWORDS

Insulin resistance;
Endometrial cancer;
Meta-analysis

Abstract *Aim:* It has been suggested that chronic hyperinsulinemia from insulin resistance is involved in the etiology of endometrial cancer (EC). We performed a systematic review and meta-analysis to assess whether insulin resistance is associated with the risk of EC.

Methods: We searched PubMed-Medline, Embase, Scopus, and Web of Science for articles published from database inception through 30th September 2014. We included all observational studies evaluating components defining insulin resistance in women with and without EC. Quality of the included studies was assessed by Newcastle–Ottawa scale. Random-effects models and inverse variance method were used to meta-analyze the association between insulin resistance components and EC.

Results: Twenty-five studies satisfied our inclusion criteria. Fasting insulin levels (13 studies, $n = 4088$) were higher in women with EC (mean difference [MD] 33.94 pmol/L, 95% confidence interval [CI] 15.04–52.85, $p = 0.0004$). No differences were seen in postmenopausal versus pre- and postmenopausal subgroup analysis. Similarly, non-fasting/fasting C-peptide levels (five studies, $n = 1938$) were also higher in women with EC (MD 0.14 nmol/L, 95%

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<http://dx.doi.org/10.1016/j.ejca.2015.08.031>

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CI 0.08–0.21, $p < 0.00001$). Homeostatic model assessment - insulin resistance (HOMA-IR) values (six studies, $n = 1859$) in EC patients were significantly higher than in women without EC (MD 1.13, 95% CI 0.20–2.06, $p = 0.02$). There was moderate-to-high heterogeneity among the included studies.

Conclusion: Currently available epidemiologic evidence is suggestive of significantly higher risk of EC in women with high fasting insulin, non-fasting/fasting C-peptide and HOMA-IR values.

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1. Introduction

Endometrial cancer (EC) is the most common female genital malignancy in developed countries, and its incidence is growing worldwide due to increases in both life expectancy and obesity prevalence. Its pathogenesis still remains poorly understood although the prevailing hypothesis is that a dominant oestrogenic environment favours EC development [1,2], and some gene variants for enzymes in sex-steroid synthesis pathways could also contribute to the hyperoestrogenic status associated with the risk of EC [3,4]. Oral contraceptives confer long-term protection against EC [5], while long-term sequential oestrogen plus progestogen use in menopause is known to increase the EC risk, and continuous combined oestrogen + progestogen therapy in menopause is known to reduce EC risk [6]. EC is substantially more frequent with extended adjuvant tamoxifen treatment while fertility drug treatments do not increase the EC risk [7,8].

Numerous epidemiological studies confirm an association between obesity and various cancer forms, including EC [9]. This malignancy has also been associated with sedentarism, type II diabetes mellitus, and polycystic ovary syndrome [10–14]. In postmenopausal women, excessive body weight and EC risk may be associated with an increased synthesis of oestrogen, insulin resistance, and inflammation [15–17]. Insulin resistance is highly prevalent among EC patients, including non-obese women [18], and hyperinsulinemia has been postulated as an EC risk factor independent of estradiol [19]. On the other hand, the insulin-sensitiser metformin decreases EC proliferation, may induce apoptosis and has positive effects on cancer clinical evolution [20]. However, the relationship between insulin resistance and EC development is poorly understood. We evaluated in a systematic review the current evidence on the effects of insulin resistance on the risk of EC and their potential translational clinical applications are also discussed.

2. Materials and methods

2.1. Data sources and searches

A comprehensive literature search was performed using PubMed-Medline, Embase, Web of Science and Scopus

from database inception through 30th September 2014. The database searches were performed independently by two authors (VP and VAB-Z). The PubMed search strategy is available as [Supplementary data](#).

The following pre-determined inclusion criteria were used: (i) observational studies evaluating the association between insulin resistance and EC, (ii) study population of patients >18 years, and (iii) study in any language. Our exclusion criteria were as follows: (i) no control group and (ii) fasting insulin, non-fasting/fasting C-peptide or homeostatic model assessment - insulin resistance (HOMA-IR) data were not available or could not be extracted for each of the study groups [21]. Controls are defined as patients without EC. Four study authors were contacted with requests for missing information. Only one study author responded with the requested data.

2.2. Study selection and data extraction

A list of retrieved articles were reviewed independently by two investigators (VP and VAB-Z) to choose potentially relevant articles, and disagreements on inclusion/exclusion were discussed and resolved by consensus. Two reviewers (VP and VAB-Z) independently extracted data from included studies. The following information was extracted: age, body mass index (BMI), menopausal status, insulin and/or C-peptide levels, method of diagnosis of EC, fasting status when blood samples were collected, and assays for quantifying insulin and C-peptide. Information on HOMA-IR (glucose \times insulin/a normalising constant) scores was also collected, whenever available. One author (AVH) reviewed the extractions for inconsistencies, and three authors (VP, VAB-Z and AVH) reached consensus.

2.3. Evaluation of study quality

The quality of the selected studies was assessed independently by two authors (VP and VAB-Z) using the Newcastle–Ottawa scale (NOS) [22]. The NOS uses two different tools for case–control and cohort studies and consists of three parameters of quality: selection, comparability and exposure/outcome assessment. The

NOS assigns a maximum of four points for selection, two points for comparability and three points for exposure or outcome. NOS scores of ≥ 7 were considered as high-quality studies and of 5–6 as moderate quality. An adapted form of the cohort NOS was used for assessing risk of bias in cross-sectional studies [23]. All discrepancies were addressed by a re-evaluation of the original article as a group (VP, VAB-Z and AVH).

2.4. Data synthesis and analysis

Our systematic review and meta-analysis follow the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses collaboration [24]. DerSimonian and Laird random-effects models and inverse variance method were used for all meta-analyses [25].

As the studies provided means of continuous outcomes, we used the mean difference (MD) to calculate summary statistics. We evaluated statistical heterogeneity using the tau-squared (Tau^2), Cochran chi-square (χ^2) and the I^2 statistic [26,27]. I^2 values of 40–60% represented a moderate level of heterogeneity. A p value of <0.1 for χ^2 was defined as indicating the presence of heterogeneity. Tau^2 provides an estimate of between-study variance in random-effects meta-analysis; a Tau^2 of >1 suggests the presence of substantial statistical heterogeneity. Publication bias was explored with the funnel plot and tested with the Egger test of funnel plot asymmetry [28]. When the median and interquartile range (IQR) were provided, the mean was estimated by the formula $x = (a + 2m + b)/4$ using the values of the median (m), P25 and P75 (a and b , respectively) and the standard deviation (SD) was estimated using $\text{SD} = \text{IQR}/1.35$ [29]. When the median and range were provided, the mean was estimated by the formula $x = (a + 2m + b)/4$ using the values of the median (m), the smallest value, and the largest value (a and b , respectively) and the SD was estimated by the formula $\text{SD} = \text{range}/4$ if the sample size was <70 and $\text{SD} = \text{range}/6$ if the sample size was >70 [30]. Insulin values were expressed as SI units ($1 \mu\text{IU}/\text{ml} = 6.945 \text{ pmol}/\text{L}$) [31]. C-peptide values were expressed as SI units ($1 \text{ ng}/\text{ml} = 0.333 \text{ nmol}/\text{L}$) [32]. We performed pre-specified subgroup analyses by study quality and by menopausal status (postmenopausal only versus pre- and postmenopausal). We used Review Manager (RevMan, version 5.0 for Windows; The Cochrane Collaboration, Oxford, UK) [33] and STATA 12 (College Station, TX, USA) for statistical analyses.

3. Results

3.1. Eligible studies

Our search identified 1903 publications (Fig. 1). After removing duplicates, 1019 articles were screened by

study titles/abstracts for relevance to study topic and inclusion/exclusion criteria. Forty-three articles remained for full-text review (Fig. 1). Twenty-five studies that reported levels of components that define insulin resistance and their association with EC in women were included in the meta-analysis [15, 19, 34–56]. The reasons for exclusion of the remaining 18 articles are listed in Fig. 1.

3.2. Study characteristics

Table 1 summarises the main characteristics of the included studies. Of the 25 studies ($n = 33,792$) included, 2 were prospective cohort studies [34–35], 21 case-control studies [15,19,36–54], and 2 cross-sectional studies [55,56]. Sample size in these studies ranged from 20 to 24,644. EC cases in the studies ranged from 1.4% to 74.1%. EC cases were identified by histopathology records in 17 studies, cancer/pathology registries in 2, and histopathology or cytology in 1, and no information was provided in 5. Study population included postmenopausal women only in 11 studies and both pre- and postmenopausal women in 14.

3.3. Quality assessment and publication bias

Using the NOS scale, all but four studies were identified as high quality (Supplementary Table 1) [39,45,49,54]. The funnel plot did not suggest the presence of publication bias (Supplementary Fig. 1). The formal test of asymmetry of this plot was not significant with Egger p -value of 0.9, 0.3 and 0.5 for studies providing information on fasting insulin, C-peptide and HOMA-IR, respectively.

3.4. Meta-analyses

Fasting insulin levels (13 studies, $n = 4088$) were significantly higher in women with EC compared to women without EC (MD 33.94 pmol/L, 95% confidence interval [CI] 15.04–52.85, $p = 0.0004$, $I^2 = 100\%$) (Fig. 2). Non-fasting/fasting C-peptide levels (five studies, $n = 1938$) were significantly higher in women with EC (MD 0.14 nmol/L, 95% CI 0.08–0.21, $p < 0.00001$, $I^2 = 42\%$) (Fig. 3). High HOMA-IR levels (six studies, $n = 1859$) were also significantly associated with women with EC (MD 1.13, 95% CI 0.20–2.06, $p = 0.02$, $I^2 = 94\%$) (Fig. 4). There was moderate-to-high heterogeneity for these associations.

3.5. Subgroup analyses

Differences in fasting insulin levels between EC and controls were larger in case–control studies than in other study designs; this difference did not reach statistical significance ($p = 0.06$) (Fig. 2). Also, differences in fasting insulin levels between EC and controls were

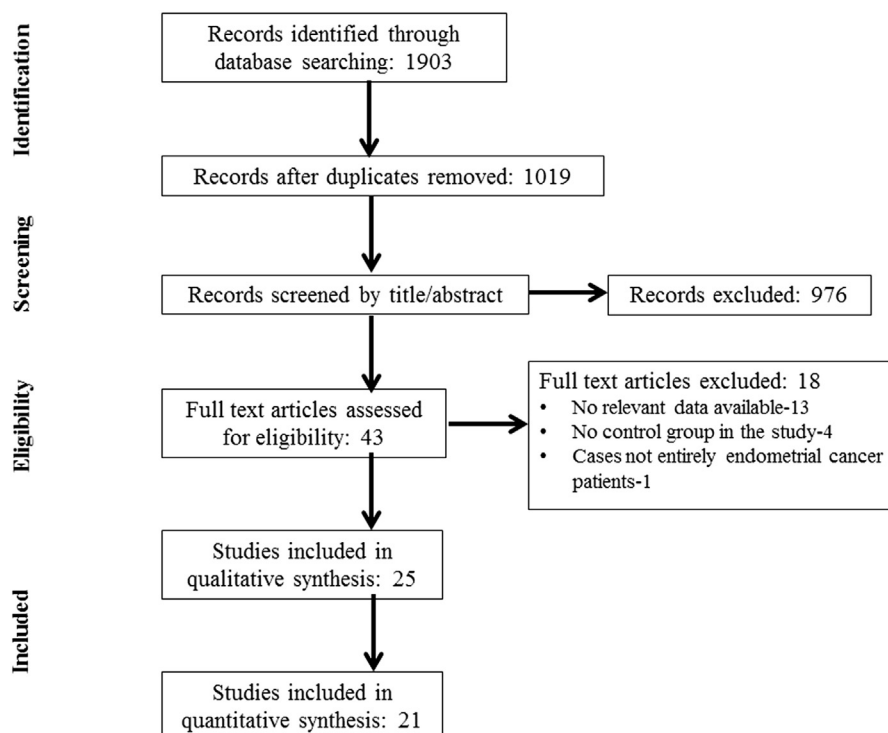


Fig. 1. Flow diagram of included studies.

larger in studies including both pre- and postmenopausal women than in those only including postmenopausal women ($p = 0.29$ for differences between subgroups); heterogeneity remained high ($I^2 = 90\%$) (Supplementary Fig. 2). Finally, high-quality studies had a smaller difference in fasting insulin levels than moderate-quality studies ($p = 0.31$ for differences between subgroups); heterogeneity remained high ($I^2 = 100\%$) (Supplementary Fig. 3).

4. Discussion

This is the first systematic review and meta-analysis to assess the role of insulin resistance in women with EC. Our meta-analysis demonstrated that there are significantly higher circulating fasting insulin and fasting/non-fasting C-peptide levels as well higher HOMA-IR values in women with EC. Available studies were heterogeneous with respect to study design, other study characteristics and the extent of the association between components of insulin resistance and EC. Our findings are in concurrence with experimental studies demonstrating the involvement of insulin in the development of malignant endometrial histological features and anchorage-independent growth [57]. A recent meta-analysis of six studies reported a significant increased risk of EC in women with metabolic syndrome (relative risk: 1.89, 95% CI 1.34–2.67) [58]. However, metabolic syndrome does not include a direct insulin estimate. In addition, during the last decade, the clinical definition of metabolic syndrome has had vast discrepancies in the

diagnosis definitions and its prevalence. Elevated circulating insulin levels have been correlated with disordered proliferative endometrium, endometrial hyperplasia and EC, and the risk increased when the HOMA-IR is ≥ 2.95 [56]. Our meta-analysis of 13 studies demonstrated that patients diagnosed with EC have a significantly higher mean insulin difference of 33.94 pmol/L as compared to women without the malignancy. Hyperinsulinism is a marker of insulin resistance and alters metabolic cell functions which consequently trigger several biochemical changes [59]. It is likely that effects of insulin resistance are more pronounced in inducing endometrial carcinogenesis in postmenopausal women, in presence of lower levels of ovarian hormones and when other metabolic factors may contribute to carcinogenesis. In fact, the prevalence of EC is higher in postmenopausal women than in women during reproductive years. However, we did not find a higher association between insulin resistance and EC in the subgroup of studies including only postmenopausal women in comparison with those studies including both pre- and postmenopausal women. This may be due to the scarcity of studies and the small numbers of women with EC in studies. Hyperinsulinism is central to pathways involving several factors including genetics, diet, body mass and obesity, inflammation, physical activity and others; a few of these have bidirectional (mutual) influences [1,2,59].

In our meta-analysis of five observational studies, we demonstrate that patients with EC have significantly higher C-peptide values as compared to women without

Table 1
Basic characteristics of included studies.

First author, year published	Study location	Study design	Study population	Sample size	EC cases (%)	Age, mean (SD)	Blood samples	Biochemical assay	EC diagnosis	Insulin resistance definition	Matched or adjusted confounders
Lucas WE, 1979 [34]	USA	PC	Postmenopausal	32	50.0	57.7 (1.9)	Fasting	RIA	Histopathology	NR	Matched for age and weight
Nagamani M, 1988 [37]	USA	CC	Postmenopausal	20	50.0	61.0	Fasting	RIA	Histopathology	NR	Matched for age, weight and years since menopause
Rutanen EM, 1993 [38]	Finland, Germany	CC	Postmenopausal	50	64.0	65.4	Fasting	RIA	Histopathology	NR	Matched for age, BMI and postmenopausal years
Gamayunova VB, 1997 [39]	Russia	CC	Pre- and postmenopausal	53	34.0	53.4 (5.3)	Fasting	RIA	NR	NR	None
Troisi R, 1997 [40]	USA	CC	Pre- and postmenopausal	345	47.8	62.4	Fasting	RIA	Histopathology	NR	Matched for age, race and zip code; adjusted for age, BMI and WTR
Anderson KE, 2001 [35]	USA	PC	Postmenopausal	24,664	1.4	61.8	NR	NR	Histopathology	NR	Adjusted for age, WHR, ovulatory span, gravidity, HRT use, HTN and menstrual irregularities
Waksmanski B, 2001 [41]	Poland	CC	Pre- and postmenopausal	48	50.0	NR	Fasting	RIA	Histopathology	NR	Matched for age and BMI
Weiderpass E, 2003 [42]	Sweden	CC	Postmenopausal	680	42.4	63.7 (7.1)	Fasting	RIA	Histopathology	NR	Matched for age groups, geography and season; adjusted for age, BMI, diabetes mellitus, physical activity, menopausal status, HRT and OCP use
Lukanova A, 2004 [43]	USA, Sweden, Italy	CC	Pre- and postmenopausal	481	34.5	NR	Fasting and non-fasting	RIA	Histopathology	NR	Matched for age, recruitment date and menopausal status; adjusted for BMI, parity, fasting status at sampling, HRT and OCP use
Cust AE, 2007 [44]	Denmark, Italy, UK, Spain, The Netherlands, Germany, France, Greece	CC	Pre- and postmenopausal	841	34.0	56.9	Fasting and non-fasting	IRMA	Histopathology	NR	Matched for study centre, menopausal status, age and time of the day at blood collection, fasting status

(continued on next page)

Table 1 (continued)

First author, year published	Study location	Study design	Study population	Sample size	EC cases (%)	Age, mean (SD)	Blood samples	Biochemical assay	EC diagnosis	Insulin resistance definition	Matched or adjusted confounders
Gunter MJ, 2008 [19]	USA	CC	Postmenopausal	715	33.6	62.9 (7.3)	Fasting	NR	Histopathology	HOMA-IR = FINS ($\mu\text{U/L}$) \times FBG (mmol/L)/22.5	Adjusted for age, BMI, estradiol, HRT use and free IGF-I
Hua SF, 2008 [45]	China	CC	Pre- and postmenopausal	85	74.1	52.0 (10.0)	Fasting	NR	NR	NR	None
Friedenreich CM, 2011 [46]	Canada	CC	Pre- and postmenopausal	1477	34.9	58.5 (9.9)	Fasting	ELISA	Histopathology	NR	Matched for age; adjusted for parity, HRT use, weight, WHR, HTN, glucose, leptin, adiponectin
Wang T, 2011 [15]	USA	CC	Postmenopausal	452	33.4	64.1 (7.4)	Fasting	NR	Histopathology	NR	None
Friedenreich CM, 2012 [47]	Canada	CC	Pre- and postmenopausal	1475	34.9	59.0	Fasting	RIA	Histopathology	NR	Matched for age; adjusted for parity, HRT use, weight, WHR, HTN, glucose, leptin, adiponectin
Modesitt SC, 2012 [48]	USA	CC	Postmenopausal	38	57.8	58.3	Fasting	ELISA	NR	NR	None
Fu JR, 2012 [49]	China	CC	Pre- and postmenopausal	65	53.9	32–71*	Fasting	ELISA, RIA, electro-chemiluminometry	NR	NR	None
Dallal CM, 2013 [50]	USA	CC	Postmenopausal	186	33.3	67.4 (5.2)	Fasting	ELISA	Cancer registry	NR	Matched for study site, age and time at blood draw
Dossus L, 2013 [36]	Denmark, Italy, UK, Spain, The Netherlands, Germany, France, Greece, Sweden	CC	Pre- and postmenopausal	679	34.3	57.7 (7.2)	Fasting	IRMA	Pathology registries	NR	Matched for study centre, menopausal status, fasting status, age at enrollment and time of day of blood collection
Erdogan S, 2013 [55]	Turkey	CS	Postmenopausal	130	46.2	52.9 (8.9)	Fasting	Chemiluminescent microparticle immunoassay	Histopathology, cytology	HOMA-IR = FINS ($\mu\text{U/L}$) \times FBG (mmol/L)/22.5	None
Ma Y, 2013 [51]	China	CC	Pre- and postmenopausal	516	39.9	53.3	Fasting	Chemiluminescent immunoassay	Histopathology	NR	Matched for age
Zhan Y, 2013 [52]	China	CC	Pre- and postmenopausal	556	37.1	53.4 (10.0)	Fasting	Chemiluminescent immunoassay	Histopathology	NR	Adjusted for age, glucose, BMI, TC, TG, HDL-C and IGFBP

Altinkaya SO, 2014 [53]	Turkey	CC	Postmenopausal	90	51.1	56.2 (11.4)	Fasting	NR	NR	Histopathology	HOMA-IR = FBG (mg/dl) × FINS (μU/ml)/405	None
Kedari GSR, 2014 [54]	India	CC	Pre- and postmenopausal	50	50.0	NR	Fasting	Chemiluminescent enzyme immunoassay	NR	NR	HOMA-IR = FBG (mmol/L) × FINS/22.5	None
Shan W, 2014 [56]	China	CS	Pre- and postmenopausal	64	39.1	45.2 (15.6)	Fasting	Electrochemiluminescent immunoassay	Histopathology	HOMA-IR = FBG (mmol/L) × FINS (μU/ml)/22.5	Adjusted for age, BMI and menopause	

EC = endometrial cancer; PC = prospective cohort; CC = case-control; CS = cross-sectional; NR = not reported; * = age range; RIA = radioimmunoassay; IRMA = immunoradiometric assay; ELISA = enzyme-linked immunosorbent assay; HOMA-IR = homeostatic model assessment - insulin resistance; FINS = fasting insulin; FBG = fasting blood glucose; BMI = body mass index; WTR = waist-to-hip ratio; WHR = waist-to-thigh ratio; HTN = hypertension, HRT = hormone replacement therapy; OCP = oral contraceptive pill; IGF-1 = insulin-like growth factor-I; HDL-C = high-density lipoprotein cholesterol; TC = serum cholesterol, TG = triglycerides; IGF1BP = insulin-like growth factor binding proteins; SD = standard deviation.

the malignancy. The lack of information on fasting time since the last meal may have led to misclassification of C-peptide levels based on fasting status and could have biased data towards the null. Higher C-peptide levels derived from insulin resistance is known to elevate the risk of non-genital cancers [60]. Proinsulin C-peptide links the A- and B-chains of insulin and facilitates different intracellular insulin synthesis steps by pancreatic β -cells. C-peptide and insulin are intracellularly stored and both released into the portal circulation in equimolar amounts. Higher C-peptide levels are observed in overweight subjects and, unlike insulin, C-peptide is not metabolised by the liver but is catabolised by the kidneys [61]. It has a longer half-life than insulin itself, reflecting more precisely the individual levels of circulating insulin when sampling has not been systematically performed in fasting conditions although blood levels are also under the influences of hepatic blood flow and extraction and BMI [62,63]. Thus, C-peptide can be considered as an indirect marker of insulin secretion. The current meta-analysis confirms and reinforces the idea that insulin resistance is associated with the EC risk.

A wide range of surrogate insulin resistance and sensitivity measures or indices have been correlated with hyperinsulinemic–euglycemic clamp, the gold standard method to assess insulin sensitivity. The glycemic load and the glycemic index influence insulin secretion and insulin-growth factors. In our meta-analysis, glucose metabolism was assessed using the HOMA-IR which estimates insulin resistance and is one of the most popular algorithms incorporating both glucose and insulin blood measurements [21]. We anticipated that HOMA-IR values might be more strongly associated with EC than individual insulin or C-peptide concentrations. This was ascertained in our pooled analysis of data from six studies which showed an MD of 1.13 HOMA-IR units, between patients with EC and women without the malignancy. Other mathematical models or indices, such as the quantitative insulin sensitivity index (QUICKI) or the Matsuda index, have been proposed as alternatives to the standard clamp and HOMA-IR studies [64]. The QUICKI is the inverse of the HOMA-IR ($\text{QUICKI} = 1/(\log(\text{fasting insulin}) \text{ in } \mu\text{U/ml} + \log(\text{fasting glucose}) \text{ in } \text{mg/dl})$) and assesses insulin sensitivity instead of insulin resistance. Abnormal QUICKI values (<0.357) have been reported in one small series of patients with EC, which was included in our meta-analysis [18]. The Matsuda index and other surrogate tests use information derived from dynamic tests after glucose or meal tolerance, but have not been reported in studies included in our systematic review.

Our study has limitations. EC is a heterogeneous disease that traditionally included two prototypes (type I and type II) based on histopathological characteristics and clinical severity, although genomic studies suggest relevant subsets of the disease [65]. We were unable to

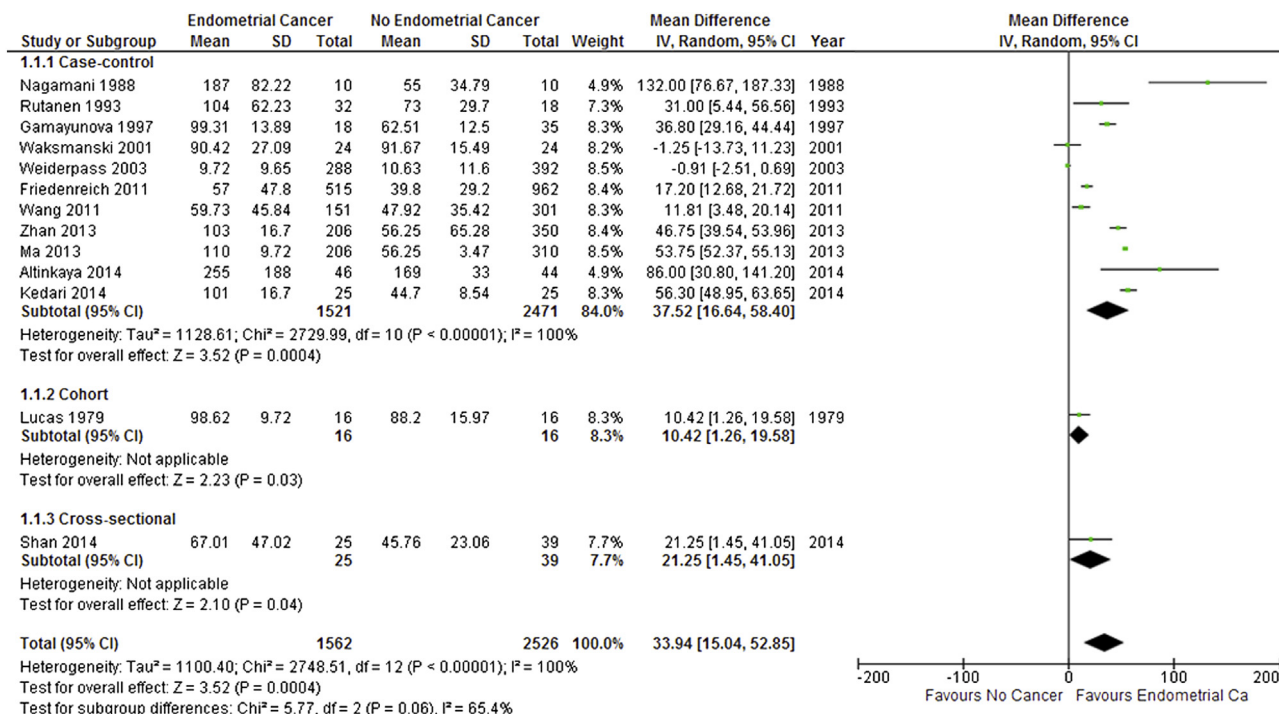


Fig. 2. Forest plot of the association between fasting insulin levels and endometrial cancer.

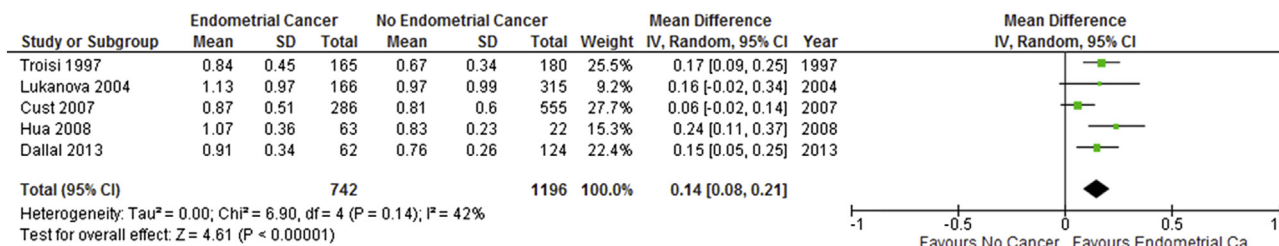


Fig. 3. Forest plot of the association between c-peptide levels and endometrial cancer.

evaluate the association of insulin resistance in EC patients based on histopathological types due to lack of data stratification by EC type in the included studies. However, both EC types share common etiologic factors

[66]. Secondly, data paucity restricted us from accounting for confounding factors such as comorbidities, anthropometry, previous hormone treatments, and lifestyle factors. In spite of this limitation,

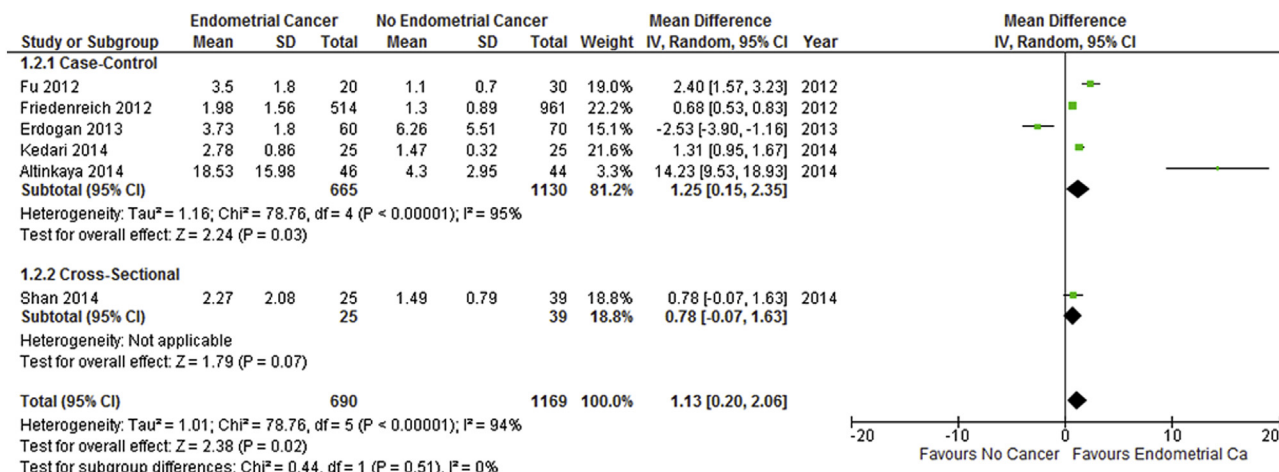


Fig. 4. Forest plot of the association between homeostatic model assessment - insulin resistance values and endometrial cancer.

our findings have strong validity as insulin resistance plays a central role in the endometrial carcinogenic process. Hyperinsulinemia enhances the subclinical inflammation status and dysregulates sex hormone production and glycemic status. Obesity may also contribute to the hyperinsulinemia and EC risk [67]. Furthermore, abdominal adiposity plays a role in creating a proinflammatory metabolic environment which could result in both insulin resistance and cancer [68]. Well-designed studies are warranted to establish these associations. Thirdly, because of lack of data on steroid hormone levels in the studied populations, we could not assess the role of insulin-related markers versus steroid hormone status. In diabetic patients, the increased levels of oestrogen and androgen and the decreasing level of progesterone are considered potentially carcinogenic conditions for the breast, endometrium and ovaries. Hyperinsulinism also indirectly produces changes in sex hormone-binding globulin (SHBG) levels, including increases in the levels of oestrogen [69]. High BMI (and hyperadiponectinemia) and non-alcoholic fatty liver may also increase circulating SHBG [70,71]. In our systematic review, only Dossus et al. [36] reported the univariable association between SHBG levels and EC and there were no studies reporting fatty liver characteristics. These factors are potential contributors of insulin resistance and endometrial carcinogenesis that should be assessed in future studies. Furthermore, insulin- and steroid-related changes may act synergistically in hormone-dependent organs. In addition, hyperinsulinemia may alter the production of insulin-like growth factor-I (IGF-I), may bind to IGF-I receptors and inhibit IGF binding protein-I (IGFBP-I) and thus further contributing to carcinogenesis [72]. Only Dossus et al [36]. evaluated the univariable association between levels of IGFBP-I and -II and EC. Therefore, we could not evaluate the association between IGFBPs and EC in a formal meta-analysis. Finally, meta-analysis of observational studies can only define associations and not causes and consequences of variables.

Impaired insulin cell response is associated to increased pancreatic beta-cell insulin secretion and circulatory hyperinsulinemia. Insulin resistance is due to both genetic and lifestyle factors, and has been associated with increased risk of metabolic syndrome, cardiovascular disease, cancer, other diseases, and mortality. Diabetes mellitus is associated with increased cancer risk [73,74]. However, limited information is available in terms of insulin resistance and risk of EC. Hyperinsulinemia can increase the levels of gonadal steroids by reducing the circulating SHBG [75], although in our systematic review there were no studies with simultaneous assessment of insulin resistance and SHBG levels. The link between anthropometric variables (height and different obesity end-points) and EC has been studied [76]. It has been proposed that obesity

favours a chronic systemic inflammatory status, reduces SHBG levels, and stimulates the IGF-I axis that would contribute to cancer progression [77–79]. Further well-designed studies are needed to define how important are our findings in the context of the current knowledge of EC [2,59,65], including anthropometric variables, body fat composition, biochemical markers such as IGF and IGFBPs, adipokines and endometrial genomic markers.

In conclusion, this comprehensive systematic review and meta-analysis demonstrate that higher fasting insulin, higher C-peptide and high HOMA-IR are associated with the risk of EC. Changes in lifestyle such as exercise, a healthy diet or selective nutrients may be recommended to improve insulin sensitivity and delay/reduce the risk of EC. Furthermore, the information provided here may support future research on the prophylactic use of an insulin sensitiser, such as metformin, or other therapeutic strategies to reduce the risk of EC in high-risk populations.

Contributors

AVH, VP, and FRP-L designed the study. AVH, VP and VAB-Z did the literature searches and designed the data extraction form. VP, VAB-Z, PT and AD extracted the data. AVH cross-checked the data extraction. VAB-Z and VP did the statistical analyses. AVH supervised the statistical analyses. FRP-L and VP wrote the paper. AVH, VP, VAB-Z, PT, AD and FRP-L critically revised subsequent drafts. All authors read and approved the submitted version.

Conflict of interest statement

AVH, VP, VAB-Z, PT, AD and FRP-L declare no relevant competing interests. AD has received research funding from 3M Incorporation.

Sources of support

None.

Acknowledgments

The authors would like to thank to Dr. Rebeca Troisi for providing additional information on C-peptide data.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejca.2015.08.031>.

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