Hyperglycemia and endometrial cancer risk

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Endometrial cancer is one of the most common cancers in women worldwide and its incidence is increasing. Epidemiological evidence shows a strong association between endometrial cancer and obesity, and multiple mechanisms linking obesity and cancer progression have been described. However, it remains unclear which factors are the main drivers of endometrial cancer development. Hyperglycemia and type 2 diabetes mellitus are common co-morbidities of obesity, and there is evidence that hyperglycemia is a risk factor for endometrial cancer independent of obesity. This review will discuss studies that have investigated the links between hyperglycemia and endometrial cancer risk.

Keywords: hyperglycemia ; HbA1c ; glucose metabolism ; uterine cancer

1. Introduction

Endometrial cancer (EC) is an adenocarcinoma that originates from the epithelial cells lining the uterine cavity. The tumor microenvironment surrounding these cells comprises stromal cells, endothelial cells [1] and many different types of immune cells [2], all of which can influence cancer progression and response to treatment. Although most ECs are early stage and confined to the uterus, others spread by invading the myometrium and metastasizing to distant sites such as lymph nodes, liver and lung [3]. According to GLOBOCAN 2018 statistics, EC is the sixth most common cancer and the 11th leading cause of cancer death in women worldwide, with 382,069 new cases and 89,929 deaths [4].

2. Classification of Endometrial Cancers

EC has been classically categorized into two clinicopathological subtypes; Type I and Type II. Type II tumors are generally more invasive, estrogen and progesterone receptor (ER/PR) negative and confer a poor prognosis; but account for less than 15% of all cases [5][6]. Type II ECs include grade 3 endometrioid, papillary serous, clear cell, and carcinosarcoma histologies [7]. In contrast, most EC cases are Type I tumors that are frequently low grade endometrioid tumors, confined to the uterus, ER/PR positive, and have higher survival rates following treatment with primary surgery [6]. Since most EC cases are Type I, the majority of studies sited in this review refer to or contain data from Type I EC, unless otherwise stated. However, recent genetic investigations have supported re-classification of EC into 4 molecular subgroups; (1) DNA-polymerase epsilon (POLE) (ultramutated), (2) microsatellite instability hypermutated, (3) copy-number low (microsatellite stable), and (4) copy-number high (serous-like) [8]. Each subgroup has prognostic significance, with the POLE group having the best prognosis (>95% progression-free survival) and the copy-number high group the worst (5-year progression-free survival of 50%). These molecular subgroups are associated with body mass index (BMI), with women in the POLE cluster having the lowest BMI and those in copy-number low cluster having the highest BMI, suggesting that obesity may impact the genetic landscape of endometrial tumors [9].

3. Risk Factors for Endometrial Cancer

Recent epidemiological studies have shown an increasing incidence of EC, especially in countries with rapid socioeconomic transitions [10]. The rate of new cases of EC is expected to rise due to an aging population and an increased prevalence of risk factors, particularly obesity [11]. In addition to obesity, a number of factors have been attributed to an increased likelihood of developing EC, including but not limited to; advancing age, late onset menopause, lower age of menarche, chronic anovulation including polycystic ovarian syndrome, estrogen therapy in the absence of progesterone, tamoxifen therapy, hereditary predisposition (Lynch syndrome), and nulliparity [12][13][14][15]. Several of these factors influence the length of time and level of exposure the uterus has to estrogen and progesterone.

A number of Mendelian Randomization (MR) studies have identified causal factors for EC (as reviewed [16][17]). MR is an analytical method that uses genetic determinants (variants), typically single nucleotide polymorphisms (SNPs), as instrumental variables for a modifiable risk factor. The MR approach is considered to be less affected by confounding factors or reverse causation but is dependent on assumptions [17]. One study showed that a genetically-predicted increase

in age of menarche, adjusted for genetically-predicted body-mass index (BMI), was associated with a lower risk of EC [18]. Another showed that variants in *CYP19A1* (the gene that encodes aromatase/estrogen synthetase) were associated with increasing estradiol levels in post-menopausal women, and risk of EC, in women of European ancestry [19]. SNPs associated with obesity (BMI), but not waist:hip ratio, were also shown to be associated with EC, indicating that obesity is a causal factor for EC [20]. Genetically-predicted higher fasting insulin levels (using 18 SNP variants) and post-challenge insulin levels (using 17 SNP variants), but not fasting glucose (using 36 SNP variants) or Type 2 diabetes (using 49 SNP variants), were associated with increased risk of EC [21] (Table 1). A more recent study by O'Mara et al. included the most numbers of cases and controls to date; 12,906 endometrial cancer cases and 108,979 country-matched controls of European ancestry [22]. This study confirmed previous findings (higher BMI associated with increased EC risk and later menarche with lower EC risk) and demonstrated that the protective effect of later menarche is partially mediated by the known relationship between lower BMI and this factor [22]. Overall, these genome-wide association studies may provide vital information to those proposing the development of a risk prediction scoring system for women at high risk of EC [23]. A scoring system such as this could enable prophylactic treatment to reduce the incidence of EC, particularly those with Type I EC [23].

Table 1. Hyperglycemia and Endometrial Cancer.

Author	Design	Population	Measure	Results
NNHSS Cohort * [24]	Prospective Cohort	24,460 women 130 EC cases	Non-fasting blood glucose	Overweight women 2.45 times more likely to be diagnosed with EC with baseline non-fasting serum glucose ≥5.6 mmol/L (RR, 95%CI 1.11–5.42). No difference in risk found in women with normal BMI.
EPIC Cohort [25]	Nested case-control	284 EC cases 546 matched control subjects	Pre-diagnosis blood glucose	Post-menopausal women 2.6 times more likely to be diagnosed with EC with higher baseline blood glucose (RR, 95%CI 1.46–4.66, $p < 0.001$). No difference in risk found in pre- or peri-menopausal women.
WHIOS Cohort [26]	Prospective Cohort	250 EC cases 465 randomly-selected controls **§**	Fasting blood glucose	Fasting serum glucose levels were not associated with EC.
Me-Can Cohort * [27]	Prospective Cohort	290,000 women 917 EC cases	Non-fasting blood glucose	Higher baseline serum glucose associated with EC in the two highest BMI quintiles (RR = 1.17, 95%CI 1.09–1.25). No association seen in lowest BMI quintiles.
AMORIS Cohort [28]	Prospective Cohort	230,737 women	Blood glucose (fasting and non-fasting)	Women with impaired glucose metabolism (6.1–6.9 mmol/L) were at 2 times increased risk of EC diagnosis than women with normal glucose metabolism (<6.1 mmol/L). Women with diabetes mellitus (≥7 mmol/L or recorded diagnosis) were 1.75 times more like to be subsequently diagnosed with EC (HRs, 95%CI 1.11–3.60 and 0.82–3.75 respectively)

Alberta Population [29]	Case-Control	541 EC cases 961 age-matched controls	Fasting blood glucose	Small association between higher baseline blood glucose and EC diagnosis (OR = 1.15, 95%CI 1.00–1.31)
SEER Medicare database [30]	Case-Control	16,323 EC cases 100,751 controls All women ≥65 years old	Impaired fasting glucose as recorded in medical notes, including type 2 diabetes diagnosis	EC risk was associated with impaired fasting glucose (OR = 1.38, 95%CI 1.29–1.42)
Vasterbotten Intervention Project [31]	Prospective Cohort	33,293 women 117 EC cases with blood glucose measurements	Fasting blood glucose and blood glucose 2 h post 75 g glucose load	Significant increasing trend in EC risk with increasing quartiles of fasting and post-load blood glucose with top versus bottom quartile RR of 1.86 (1.09–3.31, $p = 0.019$) and 1.82 (1.07–3.23, $p = 0.028$) respectively.
Modesitt et al. 2012 [32]	Case-control	38 morbidly obese women ≥50 years old scheduled for hysterectomy 22 with EC	Fasting blood glucose on morning of surgery	Significantly higher mean blood glucose in EC cases than controls (6.64 mmol/L cases vs. 5.04 mmol/L controls, $p = 0.049$)
Shou et al. 2010 [33]	Retrospective cohort	123 EC cases 90 age-matched controls	Fasting blood glucose	Significantly more cases than controls with blood glucose ≥ 5.6 mmol/L (50.4% vs. 27.8%, $p < 0.05$).
Zhan et al. 2013 [34]	Case-control	206 EC cases 350 controls	Pre-operative fasting blood glucose or type 2 diabetes diagnosis	Significantly higher mean blood glucose in EC cases than controls (6.2 vs. 5.4 mmol/L, $p < 0.001$).
Ozdemir et al. 2015 [35]	Case-control	199 women undergoing endometrial curettage for abnormal uterine bleeding 146 with normal endometrium 53 with hyperplasia or carcinoma	Fasting blood glucose	Significantly higher mean blood glucose in cases than controls (125.8 vs. 97.8 mg/dL, $p < 0.001$). Odds ratio of endometrial pathology according to fasting glucose level >88 mg/dL (4.9 mmol/L) was 0.11 (95%CI 0.03–0.3, $p < 0.001$).

Nead et al., 2015 [21]	Mendelian Randomization (MR) analysis	1287 case patients and 8273 control participants from EC studies in Australia and UK	Genetically-predicted fasting glucose levels using 36 genetic variants associated with fasting glucose	Genetically-predicted higher fasting glucose levels were not associated with EC (OR = 1.00, 95% CI = 0.67 to 1.50, $p = 0.99$).
Karaman et al., 2015 [36]	Case-control, retrospective	35 surgically staged EC patients 40 healthy controls	HbA1c levels within 3 months of hysterectomy	Significantly higher mean HbA1c in cases than controls (6.19% vs. 5.61%, $p = 0.027$).
Miao Jonasson et al., 2012 [37]	Prospective Cohort	25,476 patients with type 2 diabetes 183 cases of female genital cancer	Baseline HbA1c	No increased risk of female genital cancers with HbA1c ≥7.5% versus <7.5% No EC-specific data.
Traviar et al., 2007 [38]	Prospective Cohort	25,814 women 13 EC cases Patients with a previous diagnosis of diabetes mellitus were excluded	Baseline HbA1c	4.05 –fold increase with baseline HbA1c 6.0–6.9% (HR, 95%CI 1.10–14.88) and 5.07 –fold increase with baseline HbA1c ≥7.0% in EC risk (HR, 95%CI 1.20–21.31) compared to HbA1c <6.0%
Levran et al., 1984 [39]	Case-control	22 EC cases 939 controls of similar weight	HbA1 1-10 years after diagnosis	HbA1 was significantly increased in cases compared to controls ($p < 0.01$)

* overlapping populations. § Diabetics and patients with blood glucose > 125 mg/dL (~6.9 mmol/L) were excluded from study.

3.1. Links between Obesity and Endometrial Cancer

Worldwide, the prevalence of obesity [body mass index (BMI) > 30 kg/m^2] in women has increased five-fold in the last four decades [40]

Mechanisms linking obesity and cancer have been described in the literature [41][42]. Several of these have been proposed to link obesity to EC development and progression, including: (1) excess estrogen through aromatization of androstenedione to estradiol by adipose-derived aromatase [43], (2) altered secretion of adipokines by adipocytes, specifically lower levels of adiponectin and higher levels of leptin [44] and visfatin [45][46], (3) insulin resistance with associated hyperinsulinemia, increased insulin-like growth factor 1 (IGF-1) and decreased IGF binding protein 1 (IGFBP-1) and sex hormone binding globulin (SHBG) [44], and (4) chronic low grade inflammation from increased levels of

proinflammatory cytokines [47][48]. These mechanisms linking obesity and endometrial carcinogenesis are described elsewhere [49][50]. The role of obesity, as a component of metabolic syndrome in EC, is also described in-depth in another review [51].

3.2. Links between Hyperglycemia and Endometrial Cancer

Disorders associated with hyperglycemia (Type I and II diabetes mellitus) have an increased risk of EC, indicating that poor control of blood glucose may be an important contributor to the growth of these tumors in women. Three separate meta-analyses on this topic have demonstrated that diabetes mellitus is significantly associated with a twofold risk of developing EC [52][53][54] and several epidemiology studies have also demonstrated that this association is independent of obesity [55][56] [57](Table 1). A case-control study involving 942 cases and 1721 controls conducted by Zhang et al. demonstrated a twofold increase in EC risk in women with type II diabetes mellitus (T2DM) compared to their non-diabetic counterparts [58]. Furthermore, hyperglycemia has been associated with EC independent of obesity [59]. In a previous study by Modesitt et al. comparing women with comparable morbid obesity levels with and without Type I EC, circulating glucose levels were higher in women with cancer (119.5 vs. 90.7 mg/dl for non-cancer; $p = 0.049$) (Table 1). Interestingly, other serological factors, including estrogen and insulin, were not significantly different between the two groups . Several large prospective cohort and case-control studies have also found an increased risk of EC with higher blood glucose levels(summarized in Table 1), although the strength of these associations varies according to BMI, age, and menopausal status in some populations [24,25,27] (Table 1). One observational study did not find an association, however diabetic patients and patients with a fasting blood glucose ≥6.9 mmol/L at baseline were excluded (Table 1). Observational studies are susceptible to confounding and as such, it is possible that hyperinsulinemia, rather than hyperglycemia, is responsible for the association between T2DM and EC risk, as supported by an MR study (Table 1).

Glycosylated hemoglobin (HbA1c) is used as an indicator of blood glucose levels over the preceding 3 months [60]. In Australia, levels ≥6.5% are considered elevated [61]. While HbA1c is a more helpful indicator of long-term glycemic control than fasting or random blood glucose levels, few studies have examined the association between elevated HbA1c and EC (Table 1). However, two small case-control studies showed higher mean HbA1c in EC cases versus controls; and a prospective cohort study in a predominantly Maori population (the Indigenous people of New Zealand) found a four-to-five-fold increase in EC risk with elevated HbA1c (Table 1). Overall, there is evidence to suggest that the chronic elevation of blood glucose may increase the risk of EC.

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