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Review Article

Metabolic risk factors and mechanisms of disease in epithelial ovarian cancer: A review

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HIGHLIGHTS

- Metabolic abnormalities are associated with poor outcomes in ovarian cancer.
- The underlying mechanisms for reported negative outcomes are unclear at present.
- Cytokines, adipokines, immune cells, and signaling pathways may be involved.

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ABSTRACT

Objective. Epithelial ovarian cancer continues to be the deadliest gynecologic malignancy. Patients with both diabetes mellitus and obesity have poorer outcomes, yet research correlating metabolic abnormalities, such as metabolic syndrome, to ovarian cancer risk and outcomes is lacking. This article reviews the literature regarding metabolic derangements and their relationship to epithelial ovarian cancer, with a focus on potential mechanisms behind these associations.

Methods. PubMed and Google Scholar were searched for articles in the English language regarding epithelial ovarian cancer, obesity, diabetes mellitus, and metabolic syndrome, with a focus on studies conducted since 1990.

Results. Obesity, type II diabetes mellitus, and metabolic syndrome have been associated with poor outcomes in epithelial ovarian cancer. More studies investigating the relationship between metabolic syndrome and epithelial ovarian cancer are needed. A variety of pathologic factors may contribute to cancer risk in patients with metabolic derangements, including altered adipokine and cytokine expression, altered immune responses to tumor cells, and changes in pro-tumorigenic signaling pathways.

Conclusion. More research is needed to examine the effects of metabolic syndrome on epithelial ovarian cancer risk and mortality, as well as the underlying pathophysiologies in patients with obesity, diabetes mellitus, and metabolic syndrome that may be targeted for therapeutic intervention.

Contents

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1. Introduction

Epithelial ovarian cancer (EOC) remains the deadliest gynecologic malignancy. In 2015, there were 21,290 new cases and 14,180 deaths from this disease [1]. EOC is responsible for only 2.6% of malignancies in women, yet causes 5.1% of their cancer deaths, placing ovarian cancer as the 5th leading cause of cancer related deaths in women. Poor survival in ovarian cancer can primarily be attributed to the fact that 75% of patients present with metastatic disease beyond the pelvis [1,2]. Most prognostic factors for EOC are non-modifiable, including stage at diagnosis, age, and tumor grade. Thus, attention has become focused on modifiable risk factors for poor outcomes such as obesity, type II diabetes mellitus (DM), and other metabolic abnormalities. The prevalence of metabolic disturbances such as obesity, type II diabetes mellitus, and metabolic syndrome (MetS) has been increasing, and a growing number of studies suggest associations between each of these conditions and ovarian cancer incidence and poor outcomes [1–5].

Data from the National Health and Nutrition Examination Survey (NHANES) indicate that more than two-thirds of US adults are overweight (body mass index [BMI] ≥ 25) or obese (BMI ≥ 30); 35% are obese and 6% have a BMI > 40 [6]. Evidence for an association between obesity and an increased risk of ovarian cancer has been solidified by a meta-analysis of multiple studies (RR 1.3; 95% CI 1.1–1.5) [3]. Accompanying the rising incidence of obesity, DM is also becoming more prevalent; the World Health Organization (WHO) estimates that globally 346 million people have DM. Approximately 9% of the entire US population and 25% of adults over 65 have diabetes [7]. Among adults with DM, approximately 60% also have obesity and 80% have a BMI > 25 [8]. The link between DM and EOC incidence is debated [9]; however, DM has been clearly associated with poorer outcomes and shorter survival in EOC [4,10]. MetS is defined by the presence of three of the five following metabolic derangements in an individual: elevated waist circumference (population and country specific cutoffs), elevated triglycerides (≥150 mg/dL), reduced high-density lipoprotein cholesterol (<40 mg/dL in males, <50 mg/dL in females), hypertension (systolic ≥130, diastolic ≥85), and elevated fasting glucose (≥100 mg/dL) [11]. Estimates for MetS prevalence mirror that of obesity; approximately 38% of US adult females meet criteria for diagnosis of MetS [11,12]. According to NHANES data, approximately 65% of patients with obesity also have MetS compared to only 10% of people whose BMI is between 18.5 and 25 [12]. At present, potential associations between MetS and EOC are incompletely described.

The mechanisms linking metabolic dysregulation and ovarian cancer incidence and progression are incompletely understood. This review will focus on conveying reported correlations between metabolic abnormalities (MetS, obesity, and diabetes mellitus) and epithelial ovarian cancer incidence and mortality, and potential underlying pathophysiologic mechanisms, including changes in adipose tissue, immune function, and pro-tumorigenic signaling pathways. Fig. 1 summarizes the mechanisms that we will discuss, and illustrates possible links among metabolic disturbances, immune dysfunction, and EOC.

2. Methods

We utilized MEDLINE (PubMed) and Google Scholar to conduct an English language literature search for papers on metabolic abnormalities and their relation to EOC. Publications from January 1, 1990 until September 15, 2016 were considered. Keywords searched included “epithelial ovarian cancer”, “diabetes mellitus”, “metabolic syndrome”, “obesity”, “cancer incidence”, “metabolic risk factors”, and “ovarian cancer”. Additional publications were identified during review of the reference lists of the initial publications found.

3. Obesity and epithelial ovarian cancer

Multiple studies have examined the relationship between obesity and EOC. The Million Women Study based in the United Kingdom followed 1.2 million women for an average of 5.4 years for cancer incidence and 7.0 years for cancer mortality. This study found women with a BMI > 25 have a higher incidence of epithelial ovarian cancer compared to their normal weight counterparts (floating absolute risk (FAR) 1.13 (1.02–1.25) for BMI 27.5–29.5 (n = 349) vs. 22.5–24.9 (n = 631); FAR 1.12 (1.02–1.23) for BMI ≥ 30 (n = 438) vs. 22.5–24.9 (n = 631)). Women who were mildly overweight (BMI 25–27.4) did not have an apparent increase in risk for EOC [13]. There was an increased risk of EOC for each incremental increase in BMI (FAR 1.14 for every 10 unit increase in BMI, 95% CI 1.03–1.27). A meta-analysis by Olsen et al. also demonstrated an increased EOC risk in patients with obesity (BMI > 30, pooled effect risk 1.30, 95% CI 1.12–1.50) [3]. The same trend, although to a lesser degree, was also seen in patients who are overweight (BMI 25–29.99, OR 1.16; 95% CI 1.01–1.32). In one multivariate analysis (n = 100,418), the quartile with the largest waist-to-hip ratio (>0.89) was associated with increased risk of having epithelial ovarian cancer (age adjusted RR 1.54; CI 1.05–2.40) [14]. It has been postulated that waist-to-hip ratio might give a more accurate estimate of true visceral adiposity and thus obesity related cancer risk than BMI; however, too few studies report this measure to allow for a comprehensive analysis of this association [15].

Interestingly, the time at which obesity develops during a woman's life may impact her ovarian cancer risk. Multiple studies have demonstrated that an elevated BMI in adolescence/early adulthood increases the subsequent risk for epithelial ovarian cancer [3,14,16,17]. The Iowa

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