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Obesity-associated adipokines correlate with survival in epithelial ovarian cancer

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HIGHLIGHTS

- We predict that the leptin to adiponectin (L:A) ratio correlates with survival in ovarian cancer.
- We retrospectively evaluated the association between serum L:A ratio and survival.
- A high L:A ratio correlated with poor clinical outcome, but did not independently predict survival.

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ABSTRACT

Objectives. Obesity impacts outcome in women with epithelial ovarian cancer (EOC), although its exact role and the molecular mechanisms remain poorly defined. Adipocytes secrete leptin and adiponectin, and the leptin to adiponectin (L:A) ratio is correlated with poor survival in other malignancies. We hypothesized that the L:A ratio is associated with survival in women with EOC.

Methods. We queried the institutional tumor registry for patients with advanced stage EOC and identified a cohort of 161 women with banked fasting prediagnostic serum samples. Patients underwent cytoredutive surgery followed by platinum-based chemotherapy. Sera were assayed for leptin and adiponectin, and clinico-pathologic data were abstracted. Standard statistical tests were performed.

Results. 161 patients met inclusion criteria. We identified a significant correlation between BMI and leptin and the L:A ratio, but not adiponectin, in this cohort ($r = 0.46$, 0.46, and -0.13, respectively; $p = 0.001$, 0.001, and 0.106). Women with low L:A ratios demonstrated statistically longer disease-specific survival (57 months) compared to those with median or high levels (49 and 37 months, respectively; $p = 0.02$). On multivariate analysis, we determined that BMI and age, but not L:A ratio, retained significance as independent prognostic factors for survival ($p = 0.04$, 0.004, and 0.895, respectively).

Conclusions. In this cohort, the L:A ratio correlated statistically with clinical outcome, but did not independently predict survival. Obesity remains a modifiable risk factor in women with EOC. Further studies are needed to determine if leptin and/or adiponectin may be potential therapeutic targets in obese women with EOC.

Introduction

Epithelial ovarian cancer remains a highly fatal disease and only approximately 45% of patients are alive at 5 years after diagnosis [1]. Several prognostic factors for ovarian cancer such as age at diagnosis, stage, and grade have been well-established; however none of these are modifiable [2]. In an attempt to impact survival in this disease, several potentially modifiable factors such as obesity, smoking, alcohol consumption, use of beta blockers, and/or statins have been evaluated by our group and others [3–10].

Obesity in particular represents a modifiable risk factor that may influence disease-specific survival in ovarian cancer and this relationship has been extensively studied. However, there appears to be conflicting evidence regarding the prognostic influence of obesity on ovarian cancer survival. The most recently published meta-analysis of 14 studies on obesity and ovarian cancer concluded that although there is a suggestion that obesity is associated with a weak adverse effect on ovarian cancer survival, there is such a large amount of inter-study heterogeneity that no firm conclusions can be drawn on the subject [11]. There are several plausible reasons that may have led to the differing findings in the published literature such as modulation of chemotherapy dosing in obese patients [12]. In addition, obesity may have served as a surrogate marker in some of the positive studies for aberrant signaling pathways such as differential adipokine secretion. It is clear that the interaction between obesity and ovarian cancer survival has not been fully elucidated. Further investigation into the role of adipokines, inflammatory cytokines, and other important metabolically active molecules involved in obesity may identify a contributory link that better clarifies the relationship between obesity and ovarian cancer.

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Adipokines are peptide hormones and cytokines directly secreted by adipose tissue. Obesity leads to altered secretion of adipokines, and the dysfunctional secretion of adipokines caused by obesity is postulated to play an important role in obesity-related carcinogenesis [13]. Two of the most important adipokines are leptin and adiponectin. Leptin levels are elevated in obese patients and several *in vitro* studies have shown that leptin has both mitogenic and anti-apoptotic activity in cancer cell lines [14,15]. Conversely, adiponectin levels are decreased in obesity and it appears to have anti-carcinogenic effects [16,17]. Recently, several studies have examined the prognostic significance of the leptin to adiponectin (L:A) ratio in cancer as it has been speculated that this ratio may be more important in the development of cancer than the absolute levels of these hormones alone [18]. These studies have found that increased L:A ratios are associated with adverse outcome in colorectal, breast and endometrial cancers [19–21]. However, to our knowledge, the prognostic impact of the L:A ratio has not yet been investigated in ovarian cancer.

In this study, we hypothesized that aberrant adipokine production promotes aggressive tumor biology in advanced epithelial ovarian cancers. Our objectives were to examine the impact of the L:A ratio on survival in advanced stage epithelial ovarian cancer and to determine the relationship between the L:A ratio and established clinicopathologic prognostic factors.

Methods

The Gynecologic Oncology service at Cedars-Sinai Medical Center maintains a prospective database of all patients diagnosed with gynecologic malignancies. After obtaining IRB approval, this database was queried and all patients diagnosed with epithelial ovarian or primary peritoneal cancer from 1996 to 2006 were identified. Inclusion criteria for this study were patients with stage III or stage IV disease that had undergone primary exploratory laparotomy with the intent of complete surgical resection of metastatic disease followed by at least 6 cycles of platinum-based chemotherapy. In addition, in order to be eligible for inclusion, patients had to have available banked fasting preoperative serum and available survival and clinico-pathologic data. Patients with other malignancies, non-epithelial ovarian cancer, borderline tumors, and those who underwent neoadjuvant chemotherapy or received intraperitoneal adjuvant chemotherapy were excluded.

Optimal cytoreductive surgery was defined as residual disease of less than 1 cm. Patients with subsequent recurrent disease were treated with surgery and/or chemotherapy at the discretion of the treating physician. To obtain leptin and adiponectin levels, we assayed archived fasting serum samples from each patient using the Luminex Bead immunoassay system, a high throughput and validated immunoassay system. Medical records for all eligible patients were reviewed and abstracted data included clinico-pathologic factors such as age, stage, grade, status of cytoreductive surgery, and time to disease recurrence and death. Data were analyzed using Fisher's exact test, Kaplan–Meier survival, and Cox regression analyses. A p value of less than 0.05 was considered to be statistically significant.

Table 1
Patient characteristics.

Characteristic	Patient data (n = 161)
Median age	59 (38–79)
BMI	24 (14.3-42.5)
Stage	
III	137 (85%)
IV	24 (15%)
Grade	
2, 3	155 (96%)
Histology	
Papillary serous	150 (93%)
Cytoreductive surgery	
No residual/optimal (<1 cm)	150 (93%)
Suboptimal (≥1 cm)	11 (7%)

Table 2
Adipokine levels determined using the Luminex Bead immunoassay system.

	Range	Median
Leptin	0.01 to 74.19 ng/ml	3.75
Adiponectin	2.71 to 32.2 μg/ml	10.43
L:A ratio	0.01 to 9.94	0.35

Results

One hundred sixty one patients met criteria for inclusion. The median age in our cohort was 59 (range 38–79), and median body mass index (BMI) was 24 (range 14.3–42.5). The majority of patients had stage III disease (137 or 85%), and high grade tumor (155 or 96%) with papillary serous histology (150 or 93%). In the cohort, 150 (93%) of the patients underwent optimal cytoreductive surgery at initial exploration to <1 cm of residual disease (Table 1).

Leptin concentrations ranged from 0.01 to 74.19 ng/ml (median 3.75) and adiponectin concentrations ranged from 2.71 to 32.22 μg/ml (median 10.43). The L:A ratios ranged from 0.01 to 9.94 (median 0.35) (Table 2).

In order to determine any correlation between absolute adipokine levels and BMI, we utilized the rank correlation test. This analysis identified a statistically significant positive correlation between leptin and BMI ($r = 0.46$, $p = 0.001$). Furthermore, the rank correlation test also identified a significant positive correlation between the L:A ratio and BMI ($r = 0.46$, $p = 0.001$). Adiponectin correlated negatively with BMI in this cohort, however this did not reach statistical significance ($r = -0.13$, $p = 0.106$) (Table 3).

Subsequently, we performed a Kaplan–Meier survival analysis in order to determine if the L:A ratio correlated with survival. We divided the cohort into tertiles given that there is no established normal for the L:A ratio. Using the log rank test for trend, we found that women with low L:A ratios demonstrated statistically longer disease-specific survival (57 months) compared to those with median L:A ratios (49 months), or high L:A ratios (37 months, $p = 0.02$) (Fig. 1).

Table 3
Correlation between BMI and adipokines. We identified a significant correlation between leptin and BMI and the L:A ratio and BMI, but not between adiponectin and BMI.

	r[a]	p
Leptin and BMI	0.46	0.001
Adiponectin and BMI	-0.13	0.106
L:A ratio and BMI	0.46	0.001

[a] r = rank correlation.

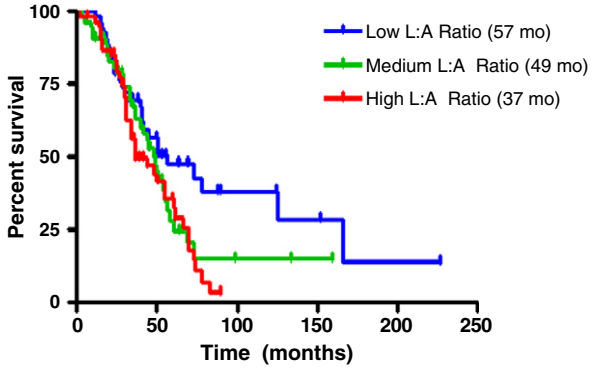

Fig. 1. Effect of the L:A ratio of disease-specific survival. Women with low L:A ratios demonstrated statistically longer disease-specific survival (57 months) compared to those with median L:A ratios (49 months), or high L:A ratios (37 months, $p = 0.02$).