

Diabetes mellitus and epithelial ovarian cancer in Chinese women: a retrospective cohort study

Can Fang^{1,*}, Yan Zhao^{2,*}, Kezhen Li¹, Danhui Weng¹, Peng Wu¹,
Gang Chen¹, Ding Ma¹, Juncheng Wei¹

¹Department of Obstetrics and Gynecology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, ²Key Laboratory for Oral Biomedical Engineering Ministry of Education, School & hospital of Stomatology, Wuhan University, Wuhan 430079 (China)

Summary

Objective: To determine whether diabetes mellitus (DM) effects progression-free survival (PFS) and overall survival (OS) in women with epithelial ovarian cancer (EOC). **Materials and Methods:** Tongji Hospital (Wuhan, China) patients presenting with EOC between 2004 and 2012 were included in a retrospective cohort study. Patients were monitored for PFS and OS through October 2014. Kaplan-Meier and log rank statistical methods were used to compare PFS and OS between diabetes mellitus patients and non-diabetic (ND) patients. **Results:** A total of 257 patients were included in the study and 64 (24.9%) were diagnosed with diabetes mellitus. Non-diabetic and diabetic mellitus patients were evenly distributed in age, malignant family history, tumor stage, pathology grade, body mass index (BMI), and protein levels of CA125. These results demonstrated that the DM group had worse PFS (31.0 vs. 44.0 months, $p = 0.008$) and OS (34.0 vs. 55.0 months, $p = 0.002$) when compared to the ND group. **Conclusion:** EOC patients with diabetes mellitus have reduced PFS and OS than patients without diabetes.

Key words: Diabetes mellitus; Epithelial ovarian cancer; Progression-free survival; Overall survival.

Introduction

Diabetes mellitus is a chronic disease characterized by high levels of glucose or hyperglycemia. The worldwide prevalence of diabetes among adults aged 20–79 years is 6.4%. Diabetes mellitus currently affects more than 285 million adults, and over the next 20 years is expected to increase by 69% in developing countries [1]. In China, 9.7% of the adult population has chronic diabetes [2]. Diabetes affects most body organs and, over time, can lead to serious complications, including nervous system damage, renal system damage, cardiovascular disease, and stroke [3].

Ovarian cancer is the seventh most common cancer and the eighth highest cause of mortality, with 239,000 new cases and 152,000 deaths in 2012 [4]. Although DM prevalence is lower in developing countries, projected ovarian cancer estimates predict there will be 52,100 new cases and 22,500 deaths in the Chinese population by 2015 [5]. Epithelial pathologies account for 90% of all ovarian cancers, and the 5-year survival rate is lower than 50% [6, 7].

Epidemiological studies suggest a negative association between DM and cancers, such as colorectal, pancreatic, bladder, endometrial, and breast cancers - increasing both the incidence and mortality rate [8–12]. The exception is prostate cancer where published studies demonstrate decreasing incidence and a positive association with DM [13]. Ovarian cancer studies suggest an association between diabetes and risk of developing cancer [14–16]. However, few

studies focused on ovarian cancer in Chinese populations and the impact DM has on PFS and OS. Therefore, a retrospective study was conducted to evaluate the impact of diabetes mellitus on survival in patients with epithelial ovarian cancer.

Materials and Methods

Patients

This study was performed under Tongji Hospital institutional review board approval. Eligible subjects were women diagnosed with epithelial ovarian cancer (EOC) receiving staging and cytoreductive surgery between 2004 to 2012. Follow up longitudinal data was collected in October 2014. Exclusion criteria were as follows: death related to cytoreductive surgery or related complications, patient's refusal, non-compliance with chemotherapy, or patients whose family couldn't provide medical data related to cancer recurrence or death.

Study design

The retrospective study objective was to evaluate whether DM impacts the survival of patients with EOC. Survival data included progression-free survival (PFS) and overall survival time (OS). PFS was calculated from the time of primary surgery until disease recurrence or death due to any cause. Disease recurrence was assessed by monitoring CA125 protein expression and tracking ovarian changes by ultrasound. The time period between pri-

*Contributed equally.

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primary surgery and death was calculated as OS. Patients who had been surviving at the end of follow up was considered censored from the survival analysis. Additional data from Tongji Hospital records were reviewed - including the presence or absence of DM, any family history of cancer, body mass index (BMI), pathological histology, tumor grade, cancer stage, and initial CA125 results before surgery. Patients with plasma glucose concentration to 7.0 mmol/l and above in subsequent testing were diagnosed as diabetes mellitus. Blood glucose testing was performed prior to surgery. Moreover, patients with a history of diabetes mellitus or record of DM treatment were included in the DM cohort. Patient weight and height before surgery were used to calculate the BMI. The final weight was corrected by subtracting the weight of ascites fluid from the total weight. Tumor histology, stage, and grade were assessed during the primary surgery. CA125 levels refer to concentrations before surgery. Familial cancer histories were recorded for three generations.

Statistical analysis

Kaplan-Meier and log rank method were used to compare PFS and OS between non-diabetes mellitus and diabetic patients. Chi-square (χ^2) test and Fisher's exact test were used to calculate categorical data - such as stage, tumor grade, histology, and family history. Wilcoxon rank-sum test was used to calculate the continuous variables (age and BMI). Cox proportional hazard model was used for multivariate analysis. All statistical analyses and survival curves were generated using IBM SPSS statistics 21 (SPSS Inc., Chicago, IL). A P-value of < 0.05 was considered statistically significant in two-tailed tests.

Results

A total of 294 patients were diagnosed between 2002 and 2014 with EOC and received surgery in Tongji Hospital. However, 10 patients died as a result of surgical complications, six patients didn't complete the required chemotherapy regimen, and 19 patients lacked supporting medical records, leaving 257 patients in the final analyses. In the 257-patient population that met inclusion criteria, 64 (24.9%) were diagnosed with DM. There was no difference in baseline characteristics between diabetes mellitus (DM) and non-diabetics group (Table 1).

In patient follow-up, women with DM had a significantly shorter median progression-free survival and overall survival compared to non-diabetic patients (31.0 vs. 44.0 months, $p = 0.008$, and 34.0 vs. 51.0, $p = 0.002$, respectively, Figure 1). In the univariate Cox analysis, the hazard ratio (HR) for association between diabetes mellitus and PFS was 1.56 (95% confidence interval, CI 1.11-2.19, $p = 0.009$). However, when adjusted by tumor grade, stage, age, histology, family history, initial CA125, and BMI, the hazard ratio was modified to 1.41 (CI 0.98-2.02, $p = 0.066$) by stage and histology. As with PFS, the association between OS and DM was 1.72 (95% CI 1.21-2.47, $p = 0.003$), and it was modified to 1.55 (95% CI 1.06-2.27, $p = 0.025$)

by stage and age. Although cancer stage was evenly distributed in the cohorts, analyses among early and advanced stage patients was carried out. Early stage referred to FIGO stage I and II (Figure 2), while advanced stage referred to FIGO stage III and Early stage patients with DM had a significantly shorter median PFS (40.0 vs. null, $p = 0.002$) and OS (50.0 vs. null, $p = 0.001$) and the median was null when the cumulative survival was above 0.5 at the end of follow up. In contrast advanced stage patients with and without DM had similar median PFS (28.0 vs. 35.0, $p = 0.372$) and OS (30.0 vs. 43.0, $p = 0.186$). In patients with early stage disease, the PFS HR was 3.43 (95% CI 1.51-7.80, $p = 0.003$) and OS HR was 4.46 (95% CI 1.65-12.07, $p = 0.003$) and were modified to 3.31 (95% CI 1.46-7.52, $p = 0.004$) and 4.32 (95% CI 1.60-11.79, $p = 0.004$) respectively. However, in patients with advanced stage disease, the PFS HR was 1.19 (95% CI 0.81-1.76, $p = 0.379$) and OS HR was 1.31 (95% CI 0.87-1.96, $p = 0.196$), and modified to 1.22 (95% CI 0.81-1.82, $p = 0.341$) and 1.33 (95% CI 0.88-2.01, $p = 0.175$), respectively.

Although this study wasn't designed to explore associations between BMI and EOC survival, the data was analyzed to see if there was a correlation between BMI and cancer. BMI was measured continuously. For each 1kg/m^2 in the univariate Cox analysis, the BMI resulted in a 2.6% lower risk of causing ovarian cancer mortality, but this result was not statistically significant (HR = 0.974, 95% CI 0.88-1.08, $p = 0.614$). When BMI cut off points were dichotomized in Chinese adults [17], patients with BMI scores of $< 24\text{ kg/m}^2$ compared equivalently to patients with an overweight BMI score of $\geq 24\text{ kg/m}^2$. The deduced association between dichotomized BMI and survival of EOC was not significant (HR = 0.958, 95% CI 0.38-2.39, $p = 0.927$) when analyzed by univariate Cox analysis.

Discussion

Although two cohort studies have already suggested an association between DM and survival of patients with EOC [18, 19], no study has been conducted in a Chinese population with unique genetic characteristics and lifestyles. Our study suggests that DM patients have lower PFS (31.0 vs. 44.0 months) and OS (34.0 vs. 55.0 months) when compared to non-diabetic patients. Shah *et al.* also concluded that EOC patients with DM had worse survival in a United States demography [18]. Diabetes mellitus confers a negative impact on progression-free survival and overall survival of patients with EOC. Our data indicate that DM is an independent risk factor among patients with early stage epithelial cancer, but in the patients with advanced stage EOC diabetes mellitus is not an independent risk factor. The Shah *et al.* study suggests a greater hazard for mortality in diabetic patients with early stage epithelial cancer, HR 4.17 versus 1.60, although not statistically significant [18]. It seems that DM affects the prognosis of epithelial ovarian cancer mainly when the cancer pathology is in an early stage. Neoplasms are localized in the early stage can-

Table 1. Patient characteristics.

	Diabetes (N = 64)	Non-diabetes (N = 193)	P-value
Age(years) ^a	51 (24,80)	51(16,82)	0.5
Initial CA 125(IU/L)	872 (11,10000)	570 (3 ,10000)	0.148
Family history (%)	6 (10.3)	15 (10.9)	0.685
BMI(kg/m ²)	19.8 (14.2, 25.3)	21.7 (15.6,30.0)	0.15
Stage (%)		0.279	
I	5 (7.8)	22 (11.4)	
II	5 (7.8)	30 (15.5)	
III	39 (60.9)	101 (52.3)	
IV	10 (15.6)	23 (11.4)	
Unknown	5 (7.8)	17 (8.8)	
Grade (%)			0.958
1	3 (4.7)	7 (3.6)	
2	5 (7.8)	15 (7.8)	
3	17 (26.6)	46 (23.8)	
Unknown	39 (60.9)	125 (64.8)	
Follow-up time (months) a	53 (23,83)	50 (22,127)	0.125
Histology (%)			0.055
Serous	52 (72.4)	138 (66.8)	
Mucinous	2 (2.3)	13 (11.3)	
Endometrioid	2 (6.9)	26 (12.1)	
Clear cell	7 (14.9)	12 (4.9)	
Others	1 (9.2)	4 (1.1)	

^a values are presented as means (minimum, maximum). BMI-body mass index.CA 125-cancer antigen 125. IU/L-international unit/liter.

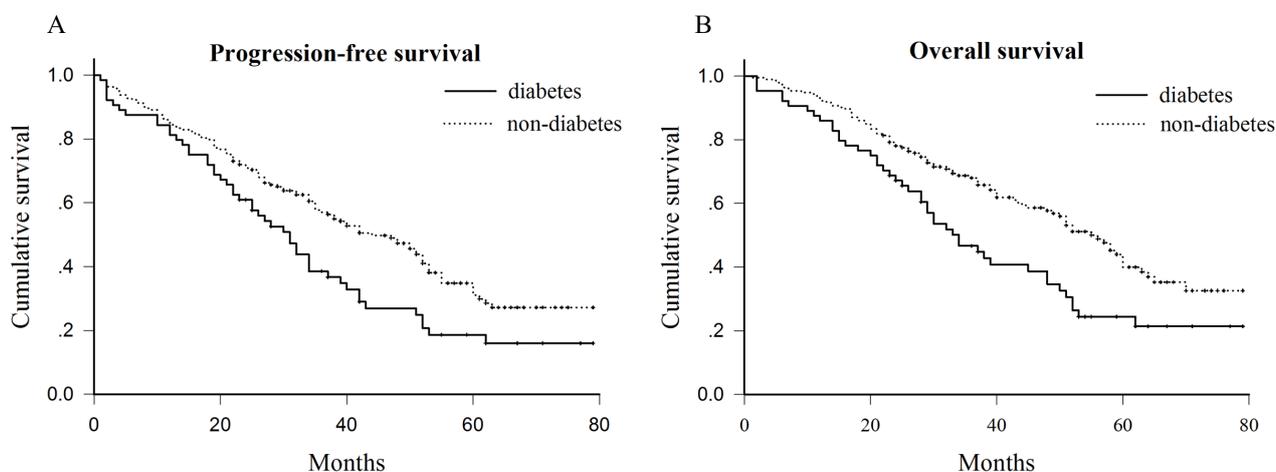


Figure 1. (A) Progression-free survival among epithelial ovarian cancer patients with versus without diabetes ($p = 0.008$). (B) Overall survival among epithelial ovarian cancer patients with versus without diabetes ($p = 0.002$)

cer, whereas advanced stage neoplasms have a tendency to extravasate and spread to distant organs. We surmise that DM may increase the propensity for tumors to invade and metastasize secondary sites.

We observed a higher prevalence of DM within our cohort (24.9%), which is higher than the previously published reports looking at the prevalence of diabetes and ovarian cancer in the general population. Studies published by Chen *et al.* and Joung *et al.* suggest no association between di-

abetes and ovarian cancer [14-16], but both diabetes and ovarian cancer are high in an aged population – a possible explanation for the higher comorbid rate of DM and EOC in the Chinese population [2, 3, 20].

The association between BMI and the survival or morbidity in EOC patients has been demonstrated in previous studies, but these studies differ in their BMI time points. Some studies record BMI years before cancer diagnosis, while others analyzed BMI post-diagnosis. Results from

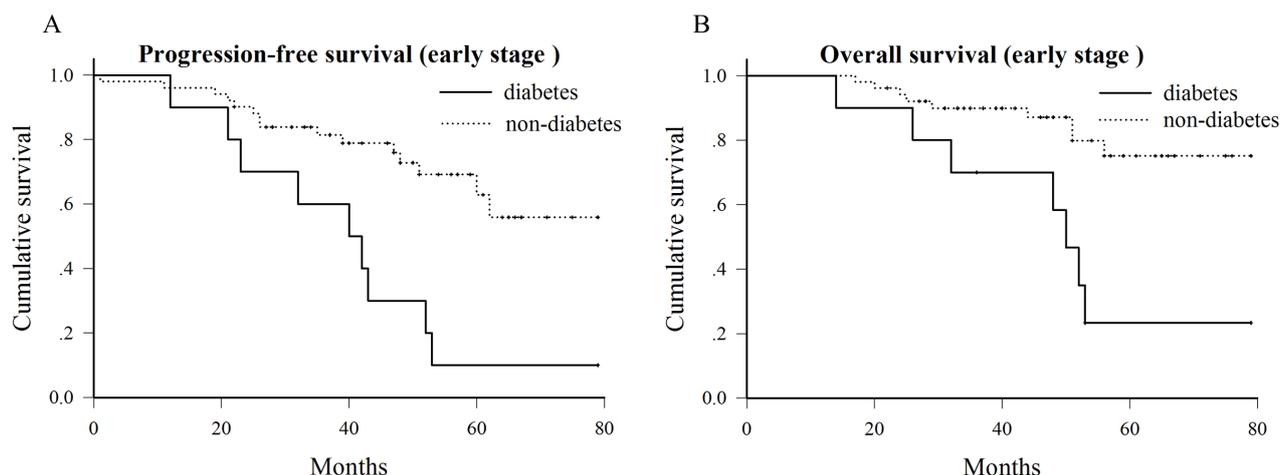


Figure 2. (A) Progression-free survival among epithelial ovarian cancer patients of early stage with versus without diabetes ($p = 0.002$). (B) Overall survival among epithelial ovarian cancer patients with versus without diabetes ($p = 0.001$).

these studies were inconsistent. For example, Zhang *et al.* found the HRs significantly increased with higher BMI at 5 years before diagnosis [21]. However, Barrett *et al.* analyzed data from a larger cohort and found obese patients with epithelial ovarian cancer did not have poor prognosis [22] when BMI was measured post diagnosis. Our study is consistent with Barrett *et al.* regardless of whether BMI was treated as continuous (OS, $p = 0.614$) or categorical (OS, $p = 0.927$).

Although epidemiological studies suggest an association between DM and cancer prognoses, the biological mechanism linking these diseases together is still unclear, though plausible mechanisms have been proposed.

First, poor prognosis in cancer patients may not be related to DM. Diabetes is known to cause nerve and renal damage, cardiovascular disease, and stroke [3], but the increased risk of mortality may stem from DM or complications associated with DM rather than cancer. However, major relevant studies analyzed the all-cause mortality only, while attribution of cause of death is often complex. In our study, neither complications nor cause of death were recorded.

Second, cancer patients with DM may present at an advanced stage and this leads to poor prognosis. Lipscombe *et al.* found that breast cancer patients with DM were more likely to present at Stage II-IV than those without diabetes in a retrospective cohort study [23]. Shah *et al.* reported EOC with DM were more likely to have stage III or greater disease [18]. We also found more stage III-IV cancers in our study, although the difference between early and late stage cancer was not statistically significant.

Third, DM may negatively impact the therapeutic response to cancer treatment. Evidence supports that cancer patients with DM have increased short-term mortality and poor response to anti-cancer treatment [24].

The last hypothesis put forth is diabetes may promote progression of cancer. Chronic type 2 diabetes is char-

acterized by hyperinsulinemia and hyperglycemia and this might be the underlying link between DM and cancer. Hyperinsulinemia reduces production of insulin like growth factor-1 (IGF-1) binding protein, and this leads to high circulating free IGF-1 [25]. Hyperinsulinemia and elevated IGF-1 bind to insulin receptor (IR) and IGF-1 receptor (IGF-1), respectively. The signaling processes downstream of IGF-1R and IR activation are similar, including ERK and PI-3K pathways [26]. Both promote cell proliferation, anti-apoptosis and cell migration, resulting in tumor development [27]. Hyperinsulinemia also leads to decreased production of sex hormone-binding globulin (SHBG), thus increasing bioavailability of estrogen. It has been reported that estrogen down-regulates nm23-H1 expression and promotes cell migration and invasion by activating the PIK3/AKT pathway in ovarian cancer [28]. Moreover, DM is characterized by inflammation [29], with elevated cytokines such as IL-6, IL-1 β [30, 31]. Increased levels of IL-6 acts as an independent predictor of poor prognosis in ovarian cancer [32].

We acknowledge several important limitations in our study. First, making a diagnosis based solely on fasting blood glucose (FBG) might lead to higher false-positives. It seems more reasonable to combine the result of oral glucose tolerance test (OGTT) with FBG for better accuracy [33]. We observed EOC was diagnosed prior to DM. EOC is known to turn on stress mechanisms, which then raises blood glucose levels. Thus, the order of pathology diagnosis (i.e. EOC first and DM second) could lead to higher false positives. Moreover, differentiating type 1 from type 2 DM could improve the Cox regression analysis, since a majority of adult patients have type 2 diabetes [34]. In addition, confounders such as complications with cytoreductive surgery, chemotherapy regimen, therapeutic sensitivities, menopause status, anti-hyperglycemic agents, and other severe comorbidities should be included in the data analysis. To statistically power the confounder study, a larger sample

cohort is needed.

Our retrospective cohort study showed that comorbid DM is strongly associated with poor outcome in EOC patients. Overall survival of cancer patients with comorbid DM averages out to a reduced life expectancy of 12 months. EOC 5-year survival is only 46% [6], but our analysis suggests that treating diabetes may positively impact the OS and prognosis of ovarian cancer patients.

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Conflict of Interest

No potential conflicts of interest were disclosed.

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Corresponding Author:

Dr. Juncheng Wei

Department of Obstetrics and Gynecology, Tongji Hospital
Tongji Medical College, Huazhong University of Science
and Technology Wuhan (China)

E-mail: wjcwjc999@126.com