

RESEARCH ARTICLE

Recurrence Season Impacts the Survival of Epithelial Ovarian Cancer Patients

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Abstract

Background: Several studies indicated that the diagnosis season affects the prognosis of some cancers, such as examples in the prostate, colon and breast. This retrospective study aimed to investigate whether the diagnosis and recurrent season impacts the prognosis of epithelial ovarian cancer patients. **Methods:** From January 2005 to August 2010, 161 epithelial ovarian cancer patients were analyzed and followed up until August 2013. Kaplan-Meier survival curves and the log-rank test were used to make the survival analysis. Multivariate analysis was conducted to identify independent prognostic factors. **Results:** The prognostic factors of overall survival in epithelial ovarian cancer patients included age, clinical stage, pathological type, histological grade, residual disease after primary surgery, recurrent season and adjuvant chemotherapy cycles. Moreover, clinical stage, histological grade, residual disease after primary surgery, recurrent season and adjuvant chemotherapy cycles also impacted the progression-free survival of epithelial ovarian cancer patients. The diagnosis season did not have a significantly relationship with the survival of operable epithelial ovarian cancer patients. Median overall survival of patients with recurrent month from April to November was 47 months, which was longer ($P < 0.001$) than that of patients with recurrence month from December to March (19 months). Median progression-free survival of patients with recurrence month from April to November and December to March was 20 and 8 months, respectively ($P < 0.001$). **Conclusion:** The recurrence season impacts the survival of epithelial ovarian cancer patients. However, the diagnosed season does not appear to exert a significant influence.

Keywords: Season - vitamin D - operable epithelial ovarian cancer - recurrence - prognosis

Asian Pac J Cancer Prev, **15** (4), 1627-1632

Introduction

Nowadays, several growth-inhibiting mechanisms in which vitamin D inhibits tumor progression and other anti-carcinogenic effects of vitamin D are under continuous research interest (Bouillon et al., 2006). Some studies indicated that vitamin D had a modulatory effect on apoptosis related genes, including up-regulation of proapoptotic genes or down-regulation of proapoptotic genes (Kizildag et al., 2010). Many previously experimental studies also reported that vitamin D promotes cell differentiation and 1,25-dihydroxyvitamin D₃ reduces the invasive potential of cancer cells in patients with metastasis. Thus, vitamin D may play an important role in the process of cancer occurrence (Mutlu et al., 2013). Vitamin D can be obtained from sun-exposure and through diets. However, exposure to sunlight, i.e., ultraviolet b (UVB), is the main source of vitamin D in humans, about 90% of all intake, is ultraviolet radiation-induced synthesis in the skin after sun exposure (Poskitt et al., 1979; Vik et al., 1980; Mainio et al., 2006; Hakko et al., 2009). Solar ultraviolet radiation is related to vitamin D status by cutaneous production of vitamin D₃ in cancer

patients (Liigant et al., 2001; Mehta et al., 2002; Robsahm et al., 2004; Porojnicu et al., 2007; Porojnicu & Robsahm et al., 2007; Hakko et al., 2009). The sunlight exposure time of spring, summer, autumn and winter was different as well as the level of vitamin D. One study demonstrated a pronounced seasonal variation of vitamin D level with a maximum in late summer and a minimum in early spring through measurements of vitamin D in healthy Danish volunteers (Mosekilde et al., 2005). During winter months, the endogenous synthesis of vitamin D₃ and the total 25-hydroxyvitamin D level in serum are up to one half of the corresponding states during the summer and autumn months (Poskitt et al., 1979; Vik et al., 1980).

Several studies indicated that the prognosis of many cancers such as lung - prostate-, breast-, colon cancer and Hodgkin lymphoma is related to the season of diagnosis (Lim et al., 2006; Porojnicu & Lagunova et al., 2007; Porojnicu et al., 2008; Mutlu et al., 2013; Oguz et al., 2013). Patients with breast cancer and colon cancer diagnosed in the summer and autumn have better survival comparing to those diagnosed in winter (Moan et al., 2005; Porojnicu & Lagunova et al., 2007), although opposite results were reported by Mutlu et al. (2013).

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Table 1. Characteristics of Patients with Epithelial Ovarian Cancer (n=161)

Characteristics	N (%)
Median age, years (range)	54 (25-84)
≤55	88 (54.7)
>55	73 (45.3)
Family history of cancer	
Yes	33 (20.5)
No	128 (79.5)
Clinical stage	
I or II	77 (47.8)
III or IV	84 (52.2)
Pathological type	
Serous	87 (54)
Non-serous	74 (46)
Histological grade	
I or II	83 (51.6)
III	78 (48.4)
Residual disease after primary surgery	
Microscopic	103 (64)
Macroscopic	58 (36)
Adjuvant chemotherapy (cycles)	
≥6	102 (63.4)
<6	59 (36.6)
Relapsed cases	87 (54)

Epithelial ovarian cancer (EOC) is the most lethal disease of the common gynecological malignancies and the leading cause of death among patients with gynecological malignancies because of its high rate of recurrence with an approximately 22,240 new cases and 14,030 deaths for 2013 (Siegel et al., 2013). However, it is controversial whether the variation of diagnosed season for ovarian cancer patients impacts the survival. Several studies have been reported the ovarian cancer mortality was reduced when diagnosed in summer (Freedman et al., 2002). As regard to ovarian cancer mortality rates and solar radiation, four studies reported higher mortality rates with lower regional sun-light (Lefkowitz et al., 1994; Freedman et al., 2002; Grant, 2002, 2003). On the other hand, one study demonstrated that no seasonal or latitudinal gradient was observed for ovarian cancer (Porojnicu et al., 2008). As a result, the relationship between ovarian cancer and the diagnosed season was inconclusive. To our knowledge, ovarian cancer has a high rate of recurrence, but there are few studies so far observed the relationship between the recurrent season and the prognosis of ovarian cancer. It is currently unclear whether recurrent season variation affects ovarian cancer survival and this association deserves further study. In our study, we retrospectively studied whether the season of epithelial ovarian cancer diagnosed and the season of recurrence impact the survival of epithelial ovarian cancer patients.

Materials and Methods

Patients

161 consecutive patients who were diagnosed with epithelial ovarian cancer at Tianjin Medical University Cancer Institute and Hospital from January 2005 to August 2010 were studied and follow up until August 2013. All the patients were operable and underwent surgery

after primary diagnosis and pathological testing for all patients were explained to confirm epithelial ovarian cancer. Postoperative residual disease was defined as “microscopic” if all visible tumor lesions were removed during primary surgery, meaning that patient with only microscopic residual tumor cells. If complete gross resection of all visible tumor lesions was not possible during primary surgery and the patient was left with residual tumor lesions of any size or number, residual disease was defined as “macroscopic”. Contrast enhanced CT, MRI, PET-CT, pathological test or CA-125 were explained to confirm patients with recurrence. And all the epithelial ovarian cancer patients did not receive surgery after relapsed. Patients were followed up every 3-6 months during the first 5 years. The patients’ medical records were reviewed and demographic, clinical and historical variables such as age, family history of cancer, operative procedure, clinical stage, pathological type, histological grade, residual disease after primary surgery, adjuvant chemotherapy and the time of death or last follow-up were derived from the medical records.

Statistical methods

The follow-up duration was calculated as the time from the date of diagnosis of epithelial ovarian cancer until the date of death or last contact. Overall survival (OS) was defined as the time from the date of diagnosis of epithelial ovarian cancer until the date of death or follow up. Progression-free survival (PFS) was calculated from the date of diagnosis of epithelial ovarian cancer to the date of tumor progression or death. To determine the appropriate cutoffs for months, the cut-point survival analysis was used. The prognostic factors which showed the potential association with OS and PFS of epithelial ovarian cancer patients were analyzed. These variables included age at the time of primary diagnosis, family history of cancer, clinical stage, pathological type, histological grade, residual disease after primary surgery, adjuvant chemotherapy. OS and PFS curves were calculated using the Kaplan-Meier method and the differences between the two groups were compared by a log-rank test. Cox proportional hazards regression was used to multivariately assess predictors of outcome. Multivariate analysis was conducted to identify independent prognostic factors. P-values of all tests less than 0.05 are taken as an indicator of statistical significance. Statistical calculations were performed by SPSS (Version: 16.0, Chicago, USA).

Results

Characteristics of patients

Baseline patients’ characteristics were summarized in Table 1. The median age at diagnosis of epithelial ovarian cancer was 54 years (range 25-84 years). Most pathological type (54%) was serous cysadenocarcinoma. Other types were endometrioid adenocarcinoma, mixed epithelial ovarian tumors, mucinous cysadenocarcinoma, clear cell carcinoma and transitional cell carcinoma. All the patients underwent primary surgery and the residual disease after surgery includes microscopic (64%) and macroscopic (36%). 102 (63.4%) epithelial ovarian cancer

Table 2. Univariate and Multivariate Analyses of Prognostic Factors for Overall Survival

	Category	Univariate	Multivariate	
		P	P	HR (95%CI)
Age	≤55y vs. >55y	0.043	0.969	1.010 (0.609-1.676)
Family history of cancer	Yes vs. No	0.232		
Clinical stage	I, II vs. III, IV	<0.001	0.003	2.786 (1.413-5.493)
Pathological type	Serous vs. Non-serous	0.035	0.015	0.522 (0.310-0.879)
Histological grade	I or II vs. III	<0.001	0.013	1.995 (1.160-3.432)
Residual disease after primary surgery	Microscopic vs. Macroscopic	<0.001	0.004	2.273 (1.295-3.989)
Adjuvant chemotherapy	≥6 cycles vs. <6 cycles	0.027	0.001	2.425 (1.451-4.053)
Recurrent season	December-March vs. April-November	<0.001	<0.001	0.274 (0.166-0.452)

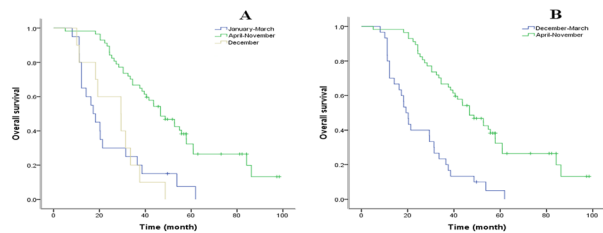


Figure 1. Overall Survival Curves for Epithelial Ovarian Cancer Patients with Different Recurrent Seasons. A. Overall survival curves for epithelial ovarian cancer patients with recurrent month from January to March, April to November, December, respectively. Median OS of January-March, April-November, December groups was 17.3, 46.7, 29.4 months, respectively. January-March group versus April-November group, $P < 0.001$; January-March group versus December group, $P = 0.980$; April-November group versus December group, $P < 0.001$. B. Overall survival curves for epithelial ovarian cancer patients with recurrent month from December to March and April to November. Median OS of December-March and April-November groups was 19.3 and 46.7 months, respectively. December-March group versus April-November group, $P < 0.001$

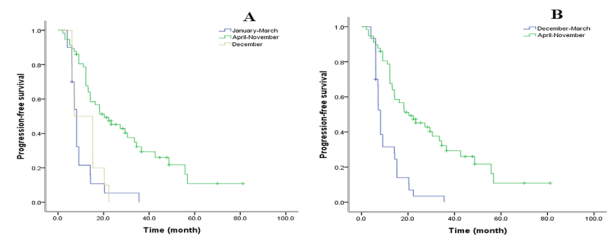


Figure 2. Progression-free Survival Curves for Epithelial Ovarian Cancer Patients with Different Recurrent Seasons. A. Progression-free survival curves for epithelial ovarian cancer patients with recurrent month from January to March, April to November, December, respectively. Median PFS of January-March, April-November, December groups was 8.2, 20.3, 7.1 months, respectively. January-March group versus April-November group, $P < 0.001$; January-March group versus December group, $P = 0.483$; April-November group versus December group, $P = 0.003$. B. Progression-free survival curves for epithelial ovarian cancer patients with recurrent month from December to March and April to November. Median PFS of December-March and April-November groups was 8.2 and 20.3 months, respectively. December-March group versus April-November group, $P < 0.001$

patients received adjuvant chemotherapy after surgery more than 6 cycles (including 6 cycles) and 59 (36.6%) patients less than 6 cycles. Among these 161 patients with epithelial ovarian cancer, 87 patients relapsed during the follow-up duration.

Diagnosis and recurrent season analysis for epithelial ovarian cancer patients

A cut-point analysis was used to determine the best cutoffs of the diagnosis and recurrent months. We selected the ability to detect differences among the subgroups based on the magnitude of the log rank test χ^2 statistic. The cut-point analysis indicated that for the primary diagnosed month of epithelial ovarian cancer there were no appropriate cutoffs for verification the statistically significantly survival differences among resulting subgroups. While the appropriate cutoffs of the recurrent month for verification the statistically significantly survival differences among resulting subgroups were April and December.

Median OS of January-March, April-November and December groups was 17.3, 46.7 and 29.4 months, respectively. By Kaplan-Meier method analysis, we found there was no survival difference between patients with recurrent month from January to March and patients with recurrent month of December ($P = 0.980$, Figure 1A).

So using the best cutoff points of April and December, patients were categorized into two groups: December-March, April-November. The median OS of December-March and April-November groups was 19.3, 46.7 months, respectively ($P < 0.001$) (Figure 1B).

Median PFS of epithelial ovarian cancer patients with recurrent month from April to November was 20.3 months, which was longer than that of patients with recurrent month from January to March (8.2 months, $P < 0.001$) and that of patients with recurrent month of December (7.1 months, $P = 0.003$). There was not significantly difference between January-March and December groups ($P = 0.483$) (Figure 2A). The median PFS of December-March group and April-November group was 8.2, 20.3 months, respectively ($P < 0.001$) (Figure 2B).

Analysis of prognostic factors

The total 161 patients were studied and analyzed by univariate analysis and demonstrated that age, clinical stage, pathological type, histological grade, residual disease after primary surgery, adjuvant chemotherapy cycles and the recurrent season could impact the OS of epithelial ovarian cancer patients. In addition, except age all these were independent prognostic factors by multivariate analysis (Table 2). Moreover, clinical stage, histological grade, residual disease after primary surgery,

Table 3. Univariate and Multivariate Analyses of Prognostic Factors for Progression-free Survival

	Category	Univariate	Multivariate	
		<i>P</i>	<i>P</i>	HR (95%CI)
Age	≤55y vs. >55y	0.067		
Family history of cancer	Yes vs. No	0.183		
Clinical stage	I, II vs. III, IV	<0.001	0.004	2.640 (1.365-5.103)
Pathological type	Serous vs. Non-serous	0.121		
Histological grade	I or II vs. III	<0.001	0.008	2.011 (1.197-3.379)
Residual disease after primary surgery	Microscopic vs. Macroscopic	<0.001	0.002	2.390 (1.377-4.149)
Adjuvant chemotherapy	≥6 cycles vs. <6 cycles	0.038	0.018	1.797 (1.107-2.917)
Recurrent season	December-March vs. April-November	<0.001	<0.001	0.291 (0.174-0.287)

Table 4. Balanced Test of Different Season Groups (total of 87 epithelial ovarian cancer patients with recurrence disease after primary surgery)

	January-March, N	April-November, N	December, N	<i>P</i>
Age (years)				0.623
≤55	8	30	5	
>55	12	27	5	
Family history of cancer				0.77
Yes	6	13	2	
No	14	44	8	
Clinical stage				0.613
I or II	4	18	3	
III or IV	16	39	7	
Pathological type				0.841
Serous	12	34	5	
Non-serous	8	23	5	
Histological grade				0.727
I or II	9	20	4	
III	11	37	6	
Residual disease after primary surgery				0.075
Microscopic	5	31	5	
Macroscopic	15	26	5	
Adjuvant chemotherapy (cycles)				0.074
≥6	9	39	4	
<6	11	18	6	

adjuvant chemotherapy cycles and the recurrent season were independent prognostic factors for PFS of patients with epithelial ovarian cancer (Table 3).

The balanced tests of all the relapsed epithelial ovarian cancer patients were made to rule out the interferences of other prognostic factors (Table 4). Using the best cutoff points of recurrent month April and December, patients were initially categorized into three groups: January-March, April-November and December. All the prognostic factors such as age, clinical stage, pathological type, histological grade, residual disease after primary surgery and adjuvant chemotherapy cycles were tested among the three groups. As a result, all the *P*-values greater than 0.05 and no significantly difference was found between the three groups.

Discussion

Epithelial ovarian cancer is the most lethal gynecologic malignancies due to frequently peritoneal widespread at the time of diagnosis or relapse (Hill et al., 2006). The recurrence of ovarian cancer remains a common event despite the relevant medical and surgical advances

achieved in the upfront treatment (Heintz et al., 2006). The primary diagnosed age, performance status, residual disease and administration of a platinum-based agent have been identified as prognostic factors for survival in patients with epithelial ovarian cancer (Hoskins, 1989; Omura et al., 1991; Hoskins et al., 1992; Thigpen et al., 1993; Hoskins et al., 1994). In our study, the prognostic factors of epithelial ovarian cancer patients include age, clinical stage, pathological type, histological grade, residual disease after primary surgery and adjuvant chemotherapy cycles. Moreover, clinical stage, histological grade, residual disease after primary surgery and adjuvant chemotherapy cycles were independent prognostic factors for PFS of patients with epithelial ovarian cancer.

Several epidemiological studies have demonstrated an association between the diagnosed season of cancer and subsequent survival, with cancer patients diagnosed in the summer and autumn months having better survival in most of these studies (Robsahm et al., 2004; Lim et al., 2006; Porojnicu et al., 2008). However, few studies have examined the association between diagnosed season and the prognosis of ovarian cancer. As regard to ovarian cancer mortality rates and solar radiation, high solar irradiance was shown to be associated with mortality rates of ovarian cancer in a worldwide study (Garland et al., 2006) while there was no association in other multinational studies (Robsahm et al., 2004; Mizoue, 2004; Tuohimaa et al., 2007). Moreover, epidemiological studies examining the relationship between dietary vitamin D and ovarian cancer also have been controversial (Bidoli et al., 2001; Salazar-Martinez et al., 2002; Goodman et al., 2002; Genkinger et al., 2006). Hence, the associations between the diagnosed season and prognosis of ovarian cancer were inconclusive.

In our study, the cut-point analysis was used to determine the best cutoffs of the diagnosed or recurrent month according the survival of epithelial ovarian cancer patients. As a result, no appropriate cutoffs were found among diagnosed months and there were no significant associations between the diagnosed season and OS or PFS of patients with operable epithelial ovarian cancer. Ovarian cancer includes various tumor types and only the patients with epithelial ovarian cancer were investigated in our study, which was different from the previous studies analyzing patients with general ovarian cancer. Moreover, all the epithelial ovarian cancer patients we analyzed were operable and underwent primary surgery, distinguishing from others studied with newly diagnosed ovarian cancer

patients. Dramatically, the recurrent season was observed could significantly impact the survival of patients with epithelial ovarian cancer and the best cut-points of the first recurrent month were April and December. Epithelial ovarian cancer patients with the recurrent month from April to November had better OS and PFS than patients with the recurrent month from December to March.

It has been suggested by studies that the underlying biological basis for the improved survival of cancer patients diagnosed in the summer and autumn months might be the exposure to sunlight and the associated higher levels of cutaneous vitamin D production at the time of diagnosis (Porojnicu et al., 2008; Roychoudhuri et al., 2009). Serum level of vitamin D varies with season, with the highest levels in the summer and autumn. Season's variation of ultraviolet B (UVB) radiation has a relationship with the incidence and mortality rates of a wide range of cancers (Hanchette et al., 1992; Grant, 2002; Turna et al., 2012). Vitamin D exerts its anti-carcinogenic properties by both inhibiting cellular proliferation, invasiveness, angiogenesis and inducing cellular differentiation, apoptosis. In other words, vitamin D could play its anti-carcinogenic role in the body existing tumor.

In conclusion, the diagnosed season for epithelial ovarian cancer had not significantly relationship with the prognosis of epithelial ovarian patients underwent primary surgery. The recurrent season observed in this study was associated with the survival of operable epithelial ovarian cancer patients. In order to unveil the mechanisms and assess the relationship between season and ovarian cancer further studies about vitamin D, exposure of sunlight and diagnosed/recurrent seasons of ovarian cancer are of great interest and deserves further investigation.

Acknowledgements

This work was supported by grants from the National Science Foundation of China (No. 81173376) and New Century Excellent Talent (NCET-11-1068). The author(s) declare that they have no competing interests.

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