Estrogen receptor and progesterone receptor status and their prognostic implications in pelvic high-grade serous carcinomas: A retrospective study

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Abstract

Background: There is mounting evidence that ovarian, tubal and peritoneal high-grade serous carcinoma (HGSC) share common origin. It was also suggested that extrauterine HGSCs may originate from endometrium. The aim of this study is to compare the estrogen receptor (ER) and progesterone receptor (PR) status among pelvic HGSCs, and to analyze the prognostic role of ER and PR in pelvic HGSCs patients, and the prognostic factors in patients with different ER or PR status

Methods: In total, 283 patients diagnosed with ovarian, tubal, peritoneal, and uterine HGSC were retrospectively analyzed. All patients' diagnosis were reviewed by a panel of gynecologists and pathologists strictly according to criteria based on lesion distribution.

Results: Patients in endometrial group were older than ovarian (60.1 ± 8.0 vs. 54.1 ± 8.3 , $p=0.000$) and tubal (60.1 ± 8.0 vs. 55.8 ± 9.5 , $p=0.008$) group. A higher proportion of ovarian group presented with advanced stage disease than fallopian and endometrial group (73.7% vs. 47.2%, $p=0.000$ and 73.7% vs. 47.4%, $p=0.002$, respectively). PR positivity rate was much lower in peritoneal compared to ovarian group (25.0% vs. 65.6%, $p=0.000$). There was no difference in survival rates among four groups. Although ER and PR were not prognostic factors for 5-year overall survival (OS) and progression-free survival (PFS), the prognostic factors were different in patients of distinct ER/PR status. More chemotherapy cycles was a protective prognostic factor in ER(+) or PR(+) patients but not in ER(-) or PR(-) patients. P53 mutation was adverse prognostic factor for OS in PR(-) patients but in PR(+) patients.

Conclusions: PR positivity rate were much lower in peritoneal compared to ovarian HGSC. Although ER and PR were not prognostic factors in pelvic HGSCs, prognostic factors for survival were different in patients of different ER/PR status.

Introduction

Ovarian, tubal, peritoneal, and endometrial high-grade serous carcinoma (HGSC) are inclusively categorized as pelvic HGSCs. Ovarian HGSC was the most common subtype of ovarian epithelial carcinomas and constitutes 60–80% of them(1). Serous carcinoma comprise 40% of tubal cancer and 70% of peritoneal cancer(2). Endometrial HGSC comprises 10~15% of endometrial cancer but account for more than 40% of endometrial cancer-related death due to its aggressive behavior and poor prognosis(3).

Although HGSC occurs in ovary and peritoneum, serous cells were not contained in these organs natively(4). The effort to identify a precursor lesion within an ovary has never been successful(5), nor has been reported in peritoneum. Fallopian tube contain native serous cells(6). Evidence has accumulated favoring a tubal origin of ovarian and peritoneal HGSCs in the past two decades. Serous tubal intraepithelial carcinoma (STIC), which was considered the precursor lesion of ovarian, tubal, and peritoneal HGSCs, was detected in 50% of female BRCA mutations carriers(6) and 35–70% of sporadic

ovarian and peritoneal HGSCs(7). Mutational analysis of these HGSCs with concurrent STIC showed identical *P53* mutations in the vast majority of cases(8).

It has also been suggested that extra-uterine HGSC may be originated from serous endometrial intraepithelial carcinoma (SEIC)(8, 9). In 21 cases of SEIC with extra-uterine HGSCs, there were 10 (48%), 5 (24%), and 6 (29%) cases had identical, discordant, and mixed *P53* mutation between SEIC and extra-uterine lesions, respectively(3). These results suggested that some of the extra-uterine HGSCs may be originated from SEIC(3).

There were few studies have compared the estrogen receptor (ER) and progesterone receptor (PR) expression among pelvic HGSCs. In the present study, we propose to compare the ER and PR status of pelvic HGSCs after systematically reviewing and conforming the cases to diagnosis criteria based on lesion distribution strictly, to inspect the hypothesis that pelvic HGSCs have common origin.

The role of ER or PR in the prognosis of ovarian HGSC patients was of dispute. ER expression was concluded to have no impact on survival outcomes of patients in a large multicenter consortium study(10), but was reported to be associated with shorter overall survival (OS) in another study(11). PR expression was reported to be associated with improved disease-specific survival (DFS) in ovarian HGSC(12). Endometrial HGSC was classified as type II endometrial cancer and was hormonally independent(10). The prognostic role of ER and PR in tubal and peritoneal HGSC patients were unclear. In the present study, we also tried to analyze the prognostic role of ER and PR in pelvic HGSCs patients, and the prognostic factors in patients with different ER or PR status.

Methods

This is a retrospective study approved by the ethics committee of the OB/GYN Hospital of Fudan University. The inclusion criteria were: (1) patients who underwent primary surgery between January 2000 and December 2012; (2) histological diagnosis of HGSC of ovary, fallopian tube, peritoneal, or uterine endometrium. The exclusion criteria were: (1) patients did not receive primary surgery in this hospital; (2) patients received neoadjuvant chemotherapy or radiotherapy before the primary surgery; (3) patients with concurrent genital or extra-genital malignancy; (4) patients had HGSC mixed with other tumor constituents such as endometrioid carcinoma or sarcoma; (5) cases with incomplete clinical documents; (6) cases cannot be assigned according to conventional diagnostic criteria (described in detail in the next paragraph).

Patients were assigned to ovarian, tubal, peritoneal, or endometrial HGSC group taking into account clinical history, surgical findings, imaging and pathological findings. The reviewing process was executed by a panel of two gynecologists and two pathologists. The diagnostic criteria for ovarian carcinoma (OC) were: (1) the disease was mainly located in the ovaries; (2) if fallopian tube was involved, the lesion should be intruded from the external serosa. Patients were assigned to tubal carcinoma (FC) if: (1) the disease was mainly located in the fallopian tube and arose from the endosalpinx; (2) the ovaries were normal or involved with lesion smaller than the tubal mass. Patients were assigned to peritoneal

carcinoma (PC) according to the Gynecologic Oncology Group criteria(13): (1) both ovaries were in normal size or enlarged for benign disease; (2) the extent of pelvic disease was greater than involving the ovaries; (3) microscopically, the ovaries showed either no tumor or tumor confined to surface, with stroma infiltration less than 5mm×5mm. Patients were diagnosed with endometrial carcinoma (EC) if: (1) HGSC was found in the uterine endometrium; (2) if the tube or ovary was involved, the lesion should be contiguous to the endometrial lesion.

In the study period, there were 171, 53, 21, and 38 cases assigned to OC, FC, PC, and EC group, respectively (Figure 1). There were 37 cases can not be assigned for the following reasons: (1) the lesions at ovaries and fallopian tubes can not be distinguished for they were jointed or wrapped together, 13 cases; (2) there were independent lesions at tubal fimbria and ovary, 10 cases; (3) there were independent lesion located at the fallopian tube and the ovary; the lesion of tube was in the luminal and not at the fimbria, 5 cases; (4) simultaneously detected lesion at the ovary and the endometrium, but the tube was not involved, 9 cases.

Patient demographic data such as menstrual information, previous history, family history, surgical treatment, chemotherapy data, follow-up of vital status, and cause of death were recorded. Reproductive duration was defined as age at natural menopausal minus menarche age for postmenopausal patients, and as age at diagnose minus menarche age for fertile women. Serum CA125 level was classified as slightly elevated ($37.2 \leq \sim < 100 \text{ U/mL}$), moderately elevated ($100 \leq \sim < 600 \text{ U/mL}$), and severely elevated ($\geq 600 \text{ U/mL}$). Surgery of the uterine corpus includes cesarean, myomectomy and hysterectomy. Surgery of the fallopian tube includes tubal ligation and [salpingectomy](#). Surgery of the ovary includes cystectomy and oophorectomy. Staging was defined according to International Federation of Gynecology and Obstetrics (FIGO) guidelines (version 2018). Satisfactory debulking surgery was defined as residual lesion $\leq 1 \text{ cm}$. Platinum-sensitivity was defined as relapse occurring ≥ 6 months after the completion of last regimen or lack of recurrence. Platinum-resistance was defined as relapse within 6 months of the completion of last regimen.

The expression of ER, PR, tumor suppressor gene protein p53 and cell proliferation index Ki-67 were evaluated using standard immunoperoxidase technique. The immunoreactivity was determined by counting the positively stained nuclei in at least 100 cells of the tumor tissue samples. ER and PR immunostaining was defined as negative when $< 5\%$ positive cells were detected in $10 \times \text{HPF}$. The p53 expression was scored semi quantitatively as 0 (no positive cells in $10 \times \text{HPF}$), 1 (0–25%), 2 (25–50%), 3 (51–75%) or 4 (75–100%). Ki-67 immunoreactivity was expressed as percentage. All the histological slides were independently reviewed by two gynecological pathologists.

Statistical analysis was performed using SPSS software (version 16.0, Chicago, IL, USA). Continuous data are expressed as mean $\pm$ standard deviation (SD). Between-group differences with respect to continuous variables were assessed by T-test or Mann-Whitney test as appropriate. Ordinal categorical variable was compared using Kruskal-Wallis H test and Mann-Whitney test. Pearson Chi-square test or Fisher's exact test was used to assess differences with respect to [categorical variables](#). Spearman's

correlation analysis was used to assess the correlation between variables and variables with $p < 0.05$ were included in the logistic regression model. OS and progression-free survival (PFS) was calculated from the date of primary surgery to death and recurrence, respectively, or the last disease-free visit. Survival analysis was performed using Kaplan-Meier and Cox regression model. All p values reported are two-tailed and a $p < 0.05$ was considered significant.

Results

Patient demographic characteristics

Age

Patients in EC group were older than OC (60.1 ± 8.0 vs. 54.1 ± 8.3 , $p = 0.000$) and FC (60.1 ± 8.0 vs. 55.8 ± 9.5 , $p = 0.008$) group (Table 1).

FIGO stage

All the patients of PC group were of FIGO stage III, thus the ratio of advanced disease (FIGO stage III and IV) were higher than the other three groups. A higher proportion of OC group presented with advanced stage disease than FC and EC group (73.7% vs. 47.2% , $p = 0.000$ and 73.7% vs. 47.4% , $p = 0.002$, respectively)(Table 1).

Gravity and parity

There was no difference of gravity between the four groups. Patients of EC group had more parity than OC group (2.1 ± 1.0 vs. 1.6 ± 0.9 , $p = 0.000$) and PC group (2.1 ± 1.0 vs. 1.7 ± 1.5 , $p = 0.017$).

Menarche age and reproductive duration

There was no difference of menarche age between the four groups. Patients of FC group had longer reproductive duration than OC group (35.1 ± 4.8 vs. 33.0 ± 4.4 years, $p = 0.004$) and PC group (35.1 ± 4.8 vs. 32.2 ± 5.9 years, $p = 0.035$) (Table 1).

Preoperative serum CA125 level

More patients of EC group presented normal CA125 level compared to OC, FC, and PC group (68.4% vs. 4.3 , $p = 0.000$, 68.4% vs. 24.5% , $p = 0.002$, and 68.4 vs. 0 , $p = 0.000$, respectively). Compared to OC group, more patients of FC group presented normal CA125 level (24.5% vs. 4.3% , $p = 0.000$).

More patients of OC group had extremely high CA125 level (≥ 600 U/ml) than FC or EC group (51.2% vs. 22.4%, $p = 0.000$ and 51.2% vs. 5.3%, $p = 0.000$, respectively). More patients of PC group had extremely high CA125 level than FC or EC group (58.8% vs. 22.4%, $p = 0.008$ and 58.8% vs. 5.3%, $p = 0.001$, respectively) (Table 1).

Spearman correlation analysis showed that CA125 level was correlated with group ($p = 0.000$), reproductive years ($p = 0.018$), stage ($p = 0.000$), and PR immunostaining ($p = 0.024$). After entering into logistic regression model, stage was the only risk factor for CA125 ($p = 0.000$). Compared to FIGO stage I, the odds ratio (OR) of stage II, III, and IV was 3.093 (95% confidence interval (CI) = 1.359–7.039), 11.038 (95%CI = 5.440–22.398), 24.607 (95%CI = 6.546–92.495), respectively.

Patient history and family history

More patients of EC group had a history of tubal ligation (28.9% vs. 11.7%, $p = 0.011$), which make major contribution to differed tubal surgery rate between two groups (31.6% vs. 14.0%, $p = 0.016$). No difference was found in uterine surgery history, ovary surgery history, tumor history of the patients themselves and their first-degree relatives (Table 2).

Surgery and chemotherapy

More patients of EC group received satisfactory debulking surgery compared to OC (94.7% vs. 70.8%, $p = 0.001$) and PC (94.7% vs. 61.9%, $p = 0.002$) group. There were 94.2%, 98.1%, 90.5%, and 97.4% of OC, TC, PC, and EC patients received platinum-based chemotherapy, respectively. Of these, 69.6%, 71.7%, 81.0%, and 81.6% patients of OC, TC, PC and EC group were sensitive to platinum-based chemotherapy, respectively. The above rates were not different among groups. Patients of OC group received more chemotherapy cycles than PC (median 6.0 vs. 3.0, $p = 0.000$) and EC (median 6.0 vs. 5.0, $p = 0.000$) group. Patients of FC group received more chemotherapy cycles than PC group (median 6.0 vs. 3.0, $p = 0.017$) (Table 3).

Immunohistochemistry

Estrogen receptor

The ER positivity rate of OC, FC, PC and EC group was 86.5%, 88.0%, 90.0%, and 75.0%, respectively. There was no difference of ER positivity rate among groups ($p > 0.05$) (Table 4).

Progesterone receptor

The PR positivity rate of OC, FC, PC and EC group was 65.6%, 50.0%, 25.0%, and 50.0%, respectively. PR positivity rate was higher in OC compared to FC and PC group ($p = 0.046$ and $p = 0.000$, respectively) (Table 4).

PR positivity was correlated with group ($p = 0.001$), age ($p = 0.000$), menarche age ($p = 0.031$), ER positivity ($p = 0.000$), and chemotherapy cycles ($p = 0.010$). After entering into logistic regression model, age (OR = 0.940, 95% CI = 0.910–0.971, $p = 0.000$), ER positivity (OR = 4.054, 95% CI = 1.874–8.771, $p = 0.000$), and group ($p = 0.010$) were the risk factors for positive PR immunostaining. The OR of OC compared to PC was 5.827 (95%CI = 1.897–17.901, $p = 0.002$).

The proliferation index Ki-67

Ki-67 immunostaining was more intensive in FC group compared to OC group (67.6 ± 19.7 vs. 57.8 ± 22.2 , $p = 0.007$) and PC group (67.6 ± 19.7 vs. 46.5 ± 28.8 , $p = 0.010$) (Table 4). However, Ki-67 immunostaining was not correlated with group but correlated with parity ($p = 0.035$), natural menopause age ($p = 0.013$), reproductive years ($p = 0.012$), and *P53* mutation status ($p = 0.034$). After entering into linear regression model, none of these factors was an independent risk factor for Ki-67 immunostaining.

P53 mutation

Normally, p53 expression was sparsely positive in nucleus, and was categorized as score 1 in the present study. *P53* mutation can manifest as either negative (nonsense mutation, score 0) or diffuse positive (missense mutation, score 2, 3, and 4). In 268 patients with *P53* information in the present study, there were 223 (83.2%) cases present with *P53* mutation. The mutation rate of *P53* was 86.4%, 84.3%, 60.0%, and 80.0% in OC, FC, PC, and EC group, respectively. There was no difference of mutation rate among these groups (Table 4).

Survival results

The rate of loss of follow-up was 13.1% (37/283) in the present study. There were 14.0% (24/171), 11.3% (6/53), 9.5% (2/21), 13.2% (5/38) patients were loss of follow-up in OC, TC, PC and EC group, respectively. The rate of loss of follow-up was not different among groups. There were 153 cases of disease-specific deaths in total. The 5-year OS rate of OC, TC, PC and EC group was 39.5%, 38.7%, 44.9%, and 53.5%, respectively. PFS rates were calculated among patients who received satisfactory debulking surgery and were sensitive to platinum-based chemotherapy (152/283, 53.7%). The 5-year PFS of OC, TC, PC and EC group was 39.0%, 48.3%, 40.0%, and 58.4%, respectively. There was no significant difference of OS or PFS among groups (Figure 2).

Prognostic factors in all HGSC patients

In the Cox regression model, useful prognostic factors for OS were FIGO stage (Hazard ratio (HR) = 2.50, 95% CI = 1.95–3.21; $p = 0.000$), unsatisfactory debulking surgery (HR = 1.78, 95% CI = 1.25–2.58; $p = 0.002$), and more chemotherapy cycles (HR = 0.89, 95% CI = 0.85–0.94; $p = 0.000$). For PFS, FIGO stage was the only useful prognostic factor (HR = 2.89, 95% CI = 2.12–3.95; $p = 0.000$). ER positivity, PR positivity, Ki67, and *P53* mutation were not prognostic factors for either OS or PFS.

Prognostic factors in HGSC patients of different ER status

In ER positive patients (N = 230), useful prognostic factor for OS in Cox regression model were FIGO stage (HR = 2.39, 95%CI = 1.82–3.14; $p = 0.000$), unsatisfactory debulking surgery (HR = 1.70, 95%CI = 1.14–2.52; $p = 0.009$), and more chemotherapy cycles (HR = 0.89, 95%CI = 0.84–0.94; $p = 0.000$). FIGO stage was the only useful prognostic factor for PFS (HR = 2.79, 95%CI = 1.96–3.99; $p = 0.000$).

In ER negative patients (N = 39), useful prognostic factors for OS were stage (HR = 3.04, 95%CI = 1.44–6.38; $p = 0.003$) and unsatisfactory debulking surgery (HR = 3.08, 95%CI = 1.20–7.90; $p = 0.020$). The only useful prognostic factors for PFS was FIGO stage (HR = 3.17, 95%CI = 1.62–6.20; $p = 0.001$) (Table 5).

Prognostic factors in HGSC patients of different PR status

In PR positive patients (N = 155), useful prognostic factor for OS in Cox regression model were stage (HR = 2.68, 95%CI = 1.96–3.67; $p = 0.000$), unsatisfactory debulking surgery (HR = 2.12, 95%CI = 1.30–3.45; $p = 0.003$), and more chemotherapy cycles (HR = 0.85, 95%CI = 0.78–0.91; $p = 0.000$). Useful prognostic factor for PFS was FIGO stage (HR = 3.08, 95%CI = 2.04–4.65; $p = 0.000$).

In PR negative patients (N = 114), useful prognostic factors for OS were FIGO stage (HR = 1.84, 95%CI = 1.28–2.65; $p = 0.001$), unsatisfactory debulking surgery (HR = 2.74, 95%CI = 1.49–5.04; $p = 0.001$), and *P53* mutation (HR = 2.54, 95%CI = 1.34–4.81; $p = 0.004$). The only useful prognostic factors for PFS was FIGO stage (HR = 2.64, 95%CI = 1.60–4.36; $p = 0.000$) (Table 6).

Discussion

In the present study, the clinical characteristics were distinct among pelvic HGSCs such as age, FIGO stage, and serum CA125 level. EC patients were older than OC and FC patients (61 vs. 54 and 61 vs. 56 years, respectively). Another study also reported patients of serous EC were older than serous OC and FC patients (68 vs. 62 and 68 vs. 63 years, respectively)(4). However, the patients in that study were 7 years older in average than that of our study. The deviance may be originated from race or other factors, which is worthy of further investigation.

It was reported that patients diagnosed with tubal and endometrial HGSC had more than 2-fold higher proportion of early-stage (FIGO stage I and II) disease compared to ovarian HGSC (35% vs.14% and 42%

vs.14%, respectively)(4). The present study had similar results. FC and EC group had about 2-fold proportion of localized disease (FIGO stage I and II) compared to OC group (52.8% vs. 26.3% and 52.6% vs. 26.3%, respectively). The difference in stage may be due to the fact that OC is typically asymptomatic in early stages; while EC patients may manifest as vaginal bleeding and FC patients may present with discharging, which facilitates visiting doctors in early stage. Serum CA125 level was also different among groups. Logistic regression model showed that advanced stage was the only risk factor for higher CA125 level.

A study based on the Surveillance, Epidemiology, and End Results (SEER) database found that tubal HGSC had better survival rates compared to ovarian, peritoneal, and uterine HGSCs(4). However, patients who did not receive surgery were included in the study and chemotherapy information of the included patients was absent. Moreover, pelvic HGSCs usually presents with metastatic and bulky multifocal disease, making the original site difficult to determine(14). But differentiation of primary site based on central clinical and pathology review was absent in that study. In the present study, we found no difference in survival among four groups. However, no difference of survival does not necessarily indicate pelvic HGSCs were of identical origin. In fact, disputes with respect to the tubal origin of PC and the endometrium-origin of extra-uterine HGSCs still exist.

Clinically, it was reported that 4.5% BRCA mutation carriers who had concurrent STIC developed peritoneal HGSC disease after risk-reducing salpingo-oophorectomy (RRSO)(15), which indicated that prophylactic RRSO failed to protect toward PC. Epidemiologically, the risk factors for serous PC differed from those for serous OC or FC in several key areas. Having a term pregnancy and breast-feeding was associated with decreased risk of OC and FC, but not of PC(16). Having a first-degree relative with breast or ovarian cancer was associated with 70% increased risk of OC, but not of PC(16). On the contrary, obesity was associated with 2-fold increased risk of PC, but not of OC or FC(16). Genetically, over-expression of HER-2 has been consistently reported to be more frequent in PC compared to OC(17). In the present study, we also found that PR positivity rate was significantly lower in PC compared to OC group (OR = 5.827 (95%CI = 1.897–17.901, p = 0.002)). These results collectively raised the possibility that serous PC may have a different aetiological pathway.

It was reported that Wilms tumor gene (WT1) was expressed in serous OC, FC, and PC, but not in serous EC(18). Another research also reported that gene expression pattern of serous OC and EC were different(19). These results suggested that serous EC was different from extra-uterine counterparts.

Although ER or PR was not independent prognostic factor for survival in pelvic HGSCs in the present study, we found that prognostic factors were different in patients with different ER or PR status. More chemotherapy cycles was a protective prognostic factor for 5-year OS in ER(+) or PR(+) patients but not in ER(-) or PR(-) patients. In PR(-) patients but not in PR(+) patients, *P53* mutation was an adverse prognostic factor for OS.

P53 mutation in the present study was assessed by immunohistochemical staining. However, a study reported that immunohistochemical staining (defining *P53* mutation as either 0% or 60–100% positive

cells) correctly identified 94% of sequencing-confirmed *P53* mutations cases(20). The authors suggested that immunohistochemical analysis is a robust surrogate for sequencing for inferring the presence of *P53* mutation(20).

The current study has inherent limitations to retrospective studies, and was carried out in a single institute with a relative small sample size. However, to our knowledge, this is the first study comparing the ER and PR status among pelvic HGSCs, and also the first study trying to compare the above parameters on the basis of systematic clinical and pathological reviewing. Moreover, this is the first study figuring the prognosis factor of pelvic HGSC patients with different ER or PR status. We found that PR status was different among pelvic HGSCs. Although ER or PR was not an prognostic factor for survival, the prognostic factors were different in patients of distinct ER/PR status. Specifically, more chemotherapy cycles was a protective prognostic factor in ER(+) or PR(+) patients but not in ER(-) or PR(-) patients. *P53* mutation was adverse prognostic factor for OS in PR(-) patients but not in PR(+) patients.

Conclusions

The PR positivity rate was much lower in peritoneal HGSC compared to ovarian HGSC patients, which cast doubts on the hypothesis that peritoneal HGSC have a common origin with ovarian HGSC. The prognosis was not different among pelvic HGSCs. Although ER and PR were not prognostic factors for survival, the prognosis factors for survival were different in patients of distinct ER/PR status. More chemotherapy cycles was a protective prognostic factor in ER(+) or PR(+) patients but not in ER(-) or PR(-) patients. *P53* mutation was adverse prognostic factor for OS in PR(-) patients but not in PR(+) patients. These results have profound clinical significance and warrant further study.

List Of Abbreviations

HGSC: high-grade serous carcinoma; STIC: Serous tubal intraepithelial carcinoma; SEIC: serous endometrial intraepithelial carcinoma; ER: estrogen receptor; PR: progesterone receptor; OS: overall survival; DFS—disease-specific survival—OC: ovarian carcinoma; FC: fallopian tubal carcinoma; PC: peritoneal carcinoma; EC: endometrial carcinoma—FIGO: International Federation of Gynecology and Obstetrics; SD: standard deviation; PFS: progression-free survival; OR: odds ratio; HR: hazards ratio; SEER—the Surveillance, Epidemiology, and End Results—RRSO—risk-reducing salpingo-oophorectomy—WT1—Wilms tumor gene.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Obstetrics and Gynecology Hospital of Fudan University (OGHFU).

Consent for publication

Not applicable.

Availability of data and material

All data supporting this study are included in this article. Please contact the corresponding author for data requests.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yuan Lu is the corresponding author contributed to the intellectual planning of the project. Hongyaun Jiang is the corresponding author reviewed data from medical records. Ting Zhao collected and reviewed data from medical records, did telephone interview of the patients, analyzed the data and wrote the manuscript. Weiyong Gu was in charge of reviewing pathological data, and Chenyun Zhang took part in reviewing the clinical data. All authors read and approved the final manuscript.

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Tables

Table 1. Patient demographic characteristics. Pairwise comparison was made and only those with a $p<0.05$ were listed in the table.
OC: ovarian carcinoma; FC: fallopian tubal carcinoma; PC: peritoneal carcinoma; EC: uterine endometrial carcinoma.

Factor	OC (N=171)	FC (N=53)	PC (N=21)	EC (N=38)	p<0.05
Age (y) (mean±SD)	54.0±8.3	56.0±9.2	57.6±11.6	61.0±8.0	OC vs. EC: p=0.000 FC vs. EC: p=0.008
FIGO stage					OC vs. FC: p=0.000
I+II (%)	45 (26.3)	28 (52.8)	0	20 (52.6)	OC vs. EC: p=0.002
III+IV (%)	126 (73.7)	25 (47.2)	21 (100)	18 (47.4)	PC vs. OC: p=0.005 PC vs. FC: p=0.000 PC vs. EC: p=0.000
Gravity (mean±SD)	2.8±1.5	2.9±1.4	3.0±1.8	3.3±1.4	
Parity (mean±SD)	1.6±0.9	1.8±1.0	1.7±1.5	2.1±1.0	OC vs. EC: p=0.000 PC vs. EC: p=0.017
Menarche age (mean±SD)	15.4±1.9	15.0±1.8	15.6±1.9	15.7±1.9	
Reproductive years (mean±SD)	33.0±4.4	35.1±4.8	32.2±5.9	34.3±4.8	OC vs. FC: p=0.004 PC vs. FC: p=0.035
CA125(U/ml)	(N=162)	(N=49)	(N=17)	(N=19)	<37.2
< 37.2(%)	7 (4.3)	12 (24.5)	0	13 (68.4)	OC vs. FC: p=0.000
37.2≤~< 100(%)	16 (9.9)	12 (24.5)	0	3 (15.8)	OC vs. EC: p=0.000
100 ≤~<600(%)	56 (34.6)	14 (28.6)	7 (41.2)	2 (10.5)	FC vs. EC: p=0.002
≥600(%)	83 (51.2)	11 (22.4)	10 (58.8)	1 (5.3)	PC vs. EC: p=0.000 ≥600 OC vs. FC: p=0.000 OC vs. EC: p=0.000 PC vs. FC: p=0.008 PC vs. EC: p=0.001

Table 2: Previous medical history and family history of the patients. Pairwise comparison was made and only those with a $p<0.05$ were listed in the table. *A patients received left tubal ligation and right salpingectomy at the same time; one patient had a relative suffered from ovarian/breast cancer and another relative diagnosed with uterine endometrioid carcinoma. OC: ovarian carcinoma; FC: fallopian tubal carcinoma; PC: peritoneal carcinoma; EC: uterine endometrial carcinoma.

History (%)	OC (N=171)	FC (N=53)	PC (N=21)	EC (N=38)	p<0.05
Uterine corpus surgery	36 (21.1)	10 (18.9)	1 (4.8)	3 (7.9)	
Cesarean	23 (13.5)	8 (15.1)	1 (4.8)	1 (2.6)	
Hysterectomy	10 (5.8)	0	0	1 (2.6)	
Myomectomy	3 (1.8)	2 (3.8)	0	1 (2.6)	
Ovarian surgery	3 (1.8)	2 (3.8)	2 (9.6)	3 (7.9)	
Cystectomy	1 (0.6)	1 (1.9)	1 (4.8)	2 (5.3)	
Oophorectomy	2 (1.2)	1 (1.9)	1 (4.8)	1 (2.6)	
Tube surgery	24* (14.0)	11 (20.8)	2 (9.6)	12 (31.6)	Tube surgery:
Tube ligation	20 (11.7)	9 (17.0)	1 (4.8)	11 (28.9)	OC vs. EC: p=0.016
Salpingectomy	5 (2.9)	2 (3.8)	1 (4.8)	1 (2.6)	Tube ligation OC vs. EC: p=0.011
Tumor history in other organs of the patient	6 (3.5)	1 (1.9)	2 (9.5)	3 (7.9)	
Breast	2 (1.2)	1 (1.9)	2 (9.5)	1 (2.6)	
Other sites	4 (2.4)	0	0	2 (5.3)	
Tumor history of first-degree relatives	15* (8.8)	3 (5.7)	1 (4.8)	1 (2.6)	
Ovarian/breast cancer	7 (4.1)	1 (1.9)	1 (4.8)	0	
Other cancers	9 (5.3)	2 (3.8)	0	1 (2.6)	

Table 3. Surgery and chemotherapy information of the patients. Pairwise comparison was made and only those with a $p<0.05$ were listed in the table. OC: ovarian carcinoma; FC: fallopian tubal carcinoma; PC: peritoneal carcinoma; EC: uterine endometrial carcinoma.

Index	OC (N=171)	FC (N=53)	PC (N=21)	EC (N=38)	p<0.05
Satisfactory debulking surgery(%)	121 (70.8%)	43 (81.1%)	13 (61.9%)	36 (94.7%)	OC vs. EC: p=0.001 PC vs. EC: p=0.002
Platinum-based chemotherapy(%)	161 (94.2)	52 (98.1%)	19 (90.5%)	37 (97.4%)	
Sensitive					
Resistant	98 (60.9)	30 (57.7)	16 (84.2)	27 (73.0)	
Unknown	19 (11.8)	8 (15.4)	1 (5.3)	2 (5.4)	
	44	14	2	8	
Chemotherapy cycles (median)	6.0	6.0	3.0	5.0	OC vs. PC: p=0.000 OC vs. EC: p=0.000 FC vs. PC: p=0.017

Table 4. Immunohistochemical staining of ER, PR, p53, and Ki-67 in the patients. Pairwise comparison was made and only those with a $p<0.05$ were listed in the table. OC: ovarian carcinoma; FC: fallopian tubal carcinoma; PC: peritoneal carcinoma; EC: uterine endometrial carcinoma.

Molecular	OC	FC	PC	EC	p<0.05
ER (%)	(N=163)	(N=50)	(N=20)	(N=36)	
(-)	22 (13.5)	6 (12.0)	2 (10.0)	9 (25.0)	
(+)	141 (86.5)	44 (88.0)	18 (90.0)	27 (75.0)	
PR (%)	(N=163)	(N=50)	(N=20)	(N=36)	OC vs. FC: p=0.046
(-)	56 (34.4)	25 (50.0)	15 (75.0)	18 (50.0)	OC vs. PC: p=0.000
(+)	107 (65.6)	25 (50.0)	5 (25.0)	18 (50.0)	
p53 (%)	(N=162)	(N=51)	(N=20)	(N=35)	
Sparse (1)	22 (13.6)	8 (15.7)	8 (40.0)	7 (20.0)	
Negative (0)	52 (32.1)	15 (29.4)	1 (5.0)	5 (14.3)	
Diffuse positive (2,3 and 4)	88 (54.3)	28 (54.9)	11 (55.0)	23 (65.7)	
<i>P53</i> mutation (%)	160 (86.4)	43 (84.3)	12 (60.0)	28 (80.0)	
Ki-67	(N=140)	(N=46)	(N=17)	(N=35)	OC vs. FC: p=0.007
(mean±SD)	57.8±22.2	67.6±19.7	46.5±28.8	60.3±23.6	FC vs. PC: p=0.010

Table 5. Hazard ratio (95%CI) of useful prognostic factors for 5-year overall survival (OS) and progression-free survival (PFS) in pelvic high-grade serous carcinoma patients of different estrogen receptor (ER) status.

ER positive (N=230)		ER negative (N=39)	
5-year OS	5-year PFS	5-year OS	5-year PFS
FIGO stage	FIGO stage	FIGO stage	FIGO stage
2.39 (1.82-3.14) (p=0.000)	2.79 (1.96-3.99) (p=0.000)	3.04 (1.44-6.38) (p=0.003)	3.17 (1.62-6.20) (p=0.001)
unsatisfactory debulking surgery		unsatisfactory debulking surgery	
1.70 (1.14-2.52) (p=0.009)		3.08 (1.20-7.90) (p=0.020)	
more chemotherapy cycles			
0.89 (0.84-0.94) (p=0.000)			

Table 6. Hazard ratio (95%CI) of useful prognostic factors for 5-year overall survival (OS) and progression-free survival (PFS) in pelvic high-grade serous carcinoma patients of different progesterone receptor (PR) status.

PR positive (N=155)		PR negative (N=114)	
5-year OS	5-year PFS	5-year OS	5-year PFS
FIGO stage	FIGO stage	FIGO stage	FIGO stage
2.68 (1.96-3.67)	3.08 (2.04-4.65)	1.84 (1.28-2.65)	2.64 (1.60-4.36)
($p=0.000$)	($p=0.000$)	($p=0.001$)	($p=0.000$)
unsatisfactory debulking surgery		unsatisfactory debulking surgery	
2.12 (1.30-3.45)		2.74 (1.49-5.04)	
($p=0.003$)		($p=0.001$)	
more chemotherapy cycles		<i>P53</i> mutation	
0.85 (0.78-0.91)		2.54 (1.34-4.81)	
($p=0.000$)		($p=0.004$)	

Figures

Figure 1

Patients included in the study OC: ovarian carcinoma; FC: fallopian tubal carcinoma; PC: peritoneal carcinoma; EC: endometrial carcinoma.

Figure 2

Survival curves for overall survival (OS) and progression-free survival (PFS) of four groups (A) OS curves for four groups. (B) PFS curve for four groups. OC: ovarian carcinoma; FC: fallopian tube carcinoma; PC: peritoneal carcinoma; EC: endometrial carcinoma.