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Sex Steroid Hormone Receptor Expression Affects Ovarian Cancer Survival[1,2]

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Abstract

Background and Aims: Although most ovarian cancers express estrogen (ER), progesterone (PR), and androgen (AR) receptors, they are currently not applied in clinical decision making. We explored the prognostic impact of sex steroid hormone receptor protein and mRNA expression on survival in epithelial ovarian cancer. *Methods:* Immunohistochemical stainings for ERα, ERβ, PR, and AR were assessed in relation to survival in 118 serous and endometrioid ovarian cancers. Expression of the genes encoding the four receptors was studied in relation to prognosis in the molecular subtypes of ovarian cancer in an independent data set, hypothesizing that the expression levels and prognostic impact may differ between the subtypes. *Results:* Expression of PR or AR protein was associated with improved 5-year progression-free ($P = .001$ for both) and overall survival ($P < .001$ for both, log-rank test). ERα and ERβ did not provide prognostic information. Patients whose tumors coexpressed PR and AR had the most favorable prognosis, and this effect was retained in multivariable analyses. Analyses of the corresponding genes using an independent data set revealed differences among the molecular subtypes, but no clear relationship between high coexpression of *PGR* and *AR* and prognosis. *Conclusions:* A favorable outcome was seen for patients whose tumors coexpressed PR and AR. Gene expression data suggested variable effects in the different molecular subtypes. These findings demonstrate a prognostic role for PR and AR in ovarian cancer and support that tumors should be stratified based on molecular as well as histological subtypes in future studies investigating the role of endocrine treatment in ovarian cancer.

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Introduction

Epithelial ovarian cancer accounts for about 3% of female cancers and is the leading cause of death from gynecologic malignancy. Although a somewhat decreased incidence and slightly improved survival have been noted during the last decades, the majority of tumors are diagnosed at advanced stages and the relative 5-year survival is less than 50% [1]. New treatment concepts have shown promising results in clinical trials, but predictive markers are needed for refined therapeutic strategies and will likely need to be stratified in relation to histopathological and molecular subtypes of ovarian cancer [2,3].

Endocrine factors play key roles in ovarian cancer development, with risk reduction related to multiparity and use of oral contraceptives [4,5]. Likewise, estrogen (ER), progesterone (PR), and androgen (AR) receptors represent prognostic markers and therapeutic targets in, e.g., breast cancer and prostate cancer [6–8]. Estrogen regulates growth and differentiation in the normal ovaries and has been demonstrated to have mutagenic effects. Progesterone, on the other hand, induces apoptosis and decreases cell membrane permeability, leading to decreased invasive potential. Progesterone may however stimulate growth at low concentrations, whereas higher concentrations seem to have growth inhibitory effects [9,10]. The majority of ovarian cancer cases are diagnosed in perimenopausal and postmenopausal women [1]. After menopause, when the estradiol level decreases, androgens are still produced and also seem to influence ovarian cancer development. Androgens promote cell proliferation, and androgen levels are decreased by the use of oral contraceptives [11]. Although the majority of ovarian cancers express ER, antiestrogen treatment has not been successful in ovarian cancer. Several studies have assessed the prognostic value of endocrine receptor expression in ovarian cancer, concluding that expression of PR is prognostically favorable, whereas the results on ERα and ERβ are contradictory. Likewise, the association with other clinical risk factors is variable [12–17]. A review and meta-analysis by Zhao et al. including in total 35 studies, of which 23 considered the prognostic value of ER, did not find any evidence of an effect of ER on prognosis [18]. Recently though, a multinational study including almost 3000 women with invasive epithelial ovarian cancer showed that ER expression was associated with improved disease-specific survival in endometrioid tumors, whereas PR expression was prognostic in serous tumors [19]. Furthermore, AR expression has been suggested to be associated with a favorable prognosis in serous ovarian tumors and is hypothesized to predict response to antiandrogen treatment [20,21]. Overall, the frequency of ER, PR, and AR expression seems to decrease with increasing malignant potential in ovarian tumors, but reports regarding covariation of the receptors are contradictory [12,16,20,22,23]. In general, however, studies of endocrine responsiveness in ovarian cancer are limited by the relatively small number of cases in each study and have not yet led to clinical application.

Ovarian cancer is a highly heterogeneous disease, and increasing evidence suggests that the different subtypes respond differently to targeted treatments and also that prognostic and predictive biomarkers may be subtype specific. In addition to the histopathological classification of ovarian cancers, gene expression profiling has revealed intrinsic molecular subtypes with additional prognostic information [24–26]. Apart from outlining the prognostic value of ER (both the α and β isoforms), PR, and AR in serous and endometrioid ovarian cancer, we aimed to explore the potential additional effect of coexpression of two or more of these receptors. We also sought to compare the immunohistochemical findings with the mRNA levels of the genes encoding each receptor in relation to the previously published molecular subtypes of ovarian cancer, using an independent data set and hypothesizing that the expression and prognostic impact of the genes encoding the sex hormone receptors may vary between the molecular subtypes. To the best of our knowledge, no reports so far have stratified for molecular subtype in relation to endocrine receptor expression in ovarian cancer, either on the mRNA or on the protein level, and this approach has the potential to further increase our knowledge of endocrine signaling in ovarian cancer.

Materials and Methods

Tumor Material

One hundred eighteen patients with epithelial serous (n = 87) and endometrioid (n = 31) ovarian cancer were included in the present study. The patients were recruited from a consecutive cohort study in the southern Swedish health care region between June 1998 and June 2000 (n = 128 patients with ovarian cancer, outlined in Malander et al. [27]) and at the oncogenetic counseling at Lund University Hospital from 1981 to 1997 (n = 18 patients). The small number of patients recruited via oncogenetic counseling reflects the limited extent of counseling service at that time. Of the 146 eligible patients, 4 patients with clear cell tumors and 10 patients with mucinous tumors were excluded because these tumors are generally not expected to express sex steroid hormone receptors [10,13]. Another 14 patients with tumors of unknown primary, mixed histologies, or undifferentiated carcinomas were excluded to reduce external factors, which may potentially bias the analyses. Of the 118 included patients, 30 (25%) had a verified *BRCA1* (n = 26) or *BRCA2* (n = 4) mutation. Detailed clinical features of included tumors are outlined in Supplementary Table S1. Tumor samples were collected at primary surgery, and the patients had not received chemotherapy before this. Information on amount of residual disease after surgery was not available. Fifty-nine of 118 (50%) patients received postoperative carboplatin (AUC5) and paclitaxel (175 mg/m^2) treatment, 18/118 (15%) received carboplatin (AUC5) and cyclophosphamide (500 mg/m^2), and 17/118 (14%) with varying disease stages were reported not to have received any postoperative chemotherapy. Information on chemotherapy treatment was missing for 24/118 (21%) patients, whereas no information on hormonal treatment was available. Eleven of 30 (37%) of the patients with *BRCA* mutations were also diagnosed with breast cancer either before or after the ovarian cancer diagnosis. All deaths within the follow-up time, however, were related to ovarian cancer. Histopathological subtypes were reviewed by a gynecological pathologist (A. M.). The histologic subtype and grade were determined according to Silverberg and WHO 2003, and hematoxylin and eosin–stained slides were used to assess tumor grade [28,29]. All tumors were staged according to the International Federation of Gynecology and Obstetrics criteria [30]. Ethical approval for the study was granted by the Lund University ethics committee (Sweden), and all patients had given their written informed consent to participate in the study.

Immunohistochemical Stainings

Existing tissue micro array (TMA) blocks were used for evaluation of protein expression by immunohistochemical staining of ERα, ERβ, PR, and AR. The construction of the TMA blocks is outlined in