RESEARCH

Sexual steroid hormone receptors profiles of ovarian carcinoma in Mexican women

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Abstract

The significance of the presence of androgen receptor (AR), estrogen receptor alpha (ER) and progesterone receptor (PR) in ovarian cancer patient survival has been a matter of numerous studies. This study was aimed to describe the expression profile of the three sexual steroid receptors in high-grade serous, endometrioid, mucinous and low-grade serous ovarian carcinoma and its association to the proliferation index in patients with primary ovarian carcinoma diagnosis, before any treatment. Eighty-one samples were obtained from the National Institute of Cancerology in Mexico City and were evaluated for the presence of AR, ER, PR and Ki67 by immunohistochemistry. The four subtypes of ovarian carcinoma displays a specific profile of the eight possible combinations of the steroid receptors with significant differences within the profile and the histological subtypes. High-grade serous carcinoma was characterized by a high frequency of both, triple-negative and AR+ ER– PR+ profiles. Endometrioid carcinoma presented a higher frequency of triple-positive profile. The presence of only AR+ profile was not observed in the endometrioid tumors. The relationship of the receptor profile with the proliferation index in the tumor epithelium shows that the expression of only ER is associated to a reduced proliferation index in endometrioid carcinoma. Steroid hormone receptor expression and co-expression could help characterize ovarian carcinoma.

Introduction

Ovarian cancer is the most lethal gynecological malignancy (1, 2). Eighty-five to ninety percent of ovarian cancers are epithelial in nature. The main histological subtypes are serous, endometrioid, mucinous and clear cells (3, 4). High-grade serous carcinoma (HGSC) is the most frequent histological subtype followed by endometrioid, mucinous, low-grade serous carcinoma (LGSC) and clear cells, although the order in the frequency of the last four subtypes varies according to the statistics of each country (5, 6, 7). Hormonal events are known to modify the development of ovarian cancer, for example, parity and oral contraceptive confer protective effects, while nulliparity and increased age are risk factors that can increase the incidence as well as tumor aggressiveness (8, 9, 10).

Sexual steroid hormones acting through their receptors regulate signaling pathways related to cell

proliferation, epithelial–mesenchymal transition, apoptosis, cell migration and invasiveness, which are essential in tumor progression (11, 12, 13, 14). The presence of androgen receptor (AR), estrogen receptor alpha (ER) and progesterone receptor (PR) plays an important role in the progression and treatment of several malignancies such as breast and endometrial cancer (15). Previous studies have reported an association between the expression of steroid receptors and the progression of ovarian cancer (16, 17, 18); however, more evidence is required to consider this association as significant in the clinical outcome of epithelial ovarian cancer. Several reports have demonstrated the expression of PR as a good prognostic biomarker in endometrioid and HGSC (17, 19, 20, 21). Androgen and ERs are highly expressed in ovarian carcinoma; nonetheless, the role of both receptors is still controversial (17, 22, 23).

The objective of this study was to determine in Mexican women the frequency of AR, ER, and PR expression in HGSC, endometrioid, mucinous and LGSC ovarian carcinoma and to describe their relationship with a cell proliferation biomarker. The present results validate previous evidence that the expression and co-expression of steroid receptors are specific for each histological subtype and could help characterize ovarian carcinomas.

Materials and methods

In this retrospective study, we evaluated the expression of AR, ER, PR and the cell proliferation biomarker Ki-67 by immunohistochemistry. We used 81 samples of ovarian carcinoma obtained from patients undergoing initial laparotomy, without any previous treatment. Samples of confirmed cases with primary ovarian carcinoma were obtained from the Tumor Bank of the National Institute of Cancerology in Mexico City (Instituto Nacional de Cancerología-INCan) from 2008 to 2016. Consent has been obtained from each patient or subject after full explanation of the purpose and nature of all procedures used. Exclusion criteria – those patients without confirmed diagnosis of primary ovarian carcinoma or refusing to sign an informed consent were not included in this study. The protocol of the study was approved by the Ethical Committees of the National Institute of Cancerology (Instituto Nacional de Cancerología-INCan 008/034/OMI) and the Faculty of Medicine from the Universidad Nacional Autónoma de México (UNAM-108/2015). Demographic and clinical characteristics of patients were obtained from the hospital clinical file.

The histological subtypes in all the cases were reviewed before being included by two pathologists of the Department of Gynecopathology. When necessary, immunohistochemistry for WT1, vimentin, hormone receptors and P53 were performed to avoid misclassification and in order to rule out metastasis.

Immunohistochemistry

Tissue microarrays constructed with a representative region (4 mm core) of the tumor selected from stained whole sections of paraformaldehyde-fixed and paraffin-embedded tissue samples, were sectioned at 3 µm thickness and placed on coated glass slides (Biocare Medical, Pacheco, CA, USA). Then the slides were deparaffinized by incubation in xylol and rehydrated through graded concentrations of ethanol. After hydration, we retrieved the antigens with Diva Decloaker (Biocare Medical) in a pressurized cooker at 110°C for 10 min; endogenous peroxidase was blocked with Peroxidazed 1 (Biocare Medical). The slides were incubated overnight at 4°C with the following polyclonal rabbit primary antibodies: anti-AR diluted 1:50 (Santa Cruz Biotechnology, Inc.), anti-ER, 1:100 (Santa Cruz Biotechnology, Inc.), anti-PR, 1:250 (Cell Signaling Technology) and anti-Ki67, 1:600 (GeneTex, Irvine, CA, USA). The secondary antibody used was Mach2 anti-rabbit HRP (Biocare Medical); signal detection was achieved with diaminobencidin chromogen kit (Biocare Medical). The negative controls were tissue samples in which the primary antibody was substituted with PBS. The positive control tissues (testis, endometrium and breast cancer) were as well included in each immune reaction.

Positive reaction for AR, ER, PR and Ki-67 was detected through nuclear staining. The samples were assessed in a double-blinded manner by two independent observers (M J G and A H M, pathologist of Hospital Militar de Especialidades de la Mujer y Neonatología). The presence of labeled epithelial cells with and *H*-score ≥30 was considered positive for each receptor (24); the proliferation index was reported as a percentage of Ki67-labeled cells measured in 200 epithelial nuclei from three separate 40× microscopic fields observed in a Nikon E600 microscope.

Statistics

The frequency of positive reactions for each receptor was evaluated with Pearson's Chi-squared test and analysis of proportions (25); the proliferation index (Ki67) by

Kruskal–Wallis and Mann–Whitney *U* tests. Statistical analysis was performed using IBM SPSS Statistics 23 (SPSS Inc.). Value of $P<0.05$ was considered significantly.

Results

Clinical characteristics of patients referred mainly from the central region of Mexico were summarized in Table 1. Differences between histological subtypes were not statistical evaluated considering the sample size.

The distribution of the four histological subtypes in ovarian carcinoma samples was HGSC, $n=29$ (36%); endometrioid, $n=29$ (36%); mucinous, $n=9$ (11%) and LGSC, $n=14$ (17%); clear cell carcinoma was not included due to the low number of cases. Immunostain for AR, ER, PR and Ki67 was observed in the nucleus of carcinoma cells (Fig. 1). The percentage of immunoreactivity for steroid receptors in the whole population was as follows AR 44/81 (54.3%), ER 32/81 (39.5%) and PR 40/81 (49.4%).

The percentage of positive nuclear immunostaining varied within the four histological subtypes; ER was present in 16/29 of the endometrioid carcinomas, significantly higher than the frequency observed in HGSC 7/29. The presence of PR is remarkably reduced in mucinous carcinomas 1/9 when compared to the other three histological subtypes. On the other hand, the presence of AR is similar in all histological subtypes, with a tendency to increase in LGSC (Fig. 2).

Co-expression of steroid receptors

Receptor profile expression in each histological subtype of ovarian carcinoma has been analyzed considering the eight possible combinations of AR, ER and PR (Fig. 3). HGSC was characterized by a high frequency of both triple-negative and AR+ ER– PR+ profiles; while, triple-positive and AR– ER+PR+ were the less frequent profiles (Fig. 3A). Endometrioid carcinoma presented a higher frequency of triple-positive profile compared with HGSC and mucinous carcinoma. The presence of AR+ ER– PR– profile was not observed in the endometrioid tumors (Fig. 3B). In mucinous carcinoma, the number of cases is relatively low to define a complete profile; however, the triple-negative profile predominates and 7/9 of mucinous carcinomas presented none or only one receptor (Fig. 3C). On the other hand, LGSC displayed a low frequency of triple negative, but a higher frequency of AR+ ER–PR+ combination (Fig. 3D).

Proliferation index

The proliferation index of each tumor was simultaneously evaluated by immunohistochemistry for Ki67 and expressed as the percentage of positive epithelial cells. When comparing the proliferation index within the histological subtypes, we found a significant association ($P=0.002$). The highest proliferation index corresponded to HGSC, while mucinous carcinoma presented the lowest proliferation index (Table 2).

The proliferation index obtained in the eight possible combinations of the three sexual steroid receptors is represented in Table 3. Only HGSC and endometrioid carcinomas have been represented because of the low number of carcinomas corresponding to the other subtypes. When ER was the only receptor expressed (AR– ER+ PR–) in endometrioid carcinomas, the proliferation index was reduced compared to those that

Table 1 Clinical characteristic of patients with histological subtypes of ovarian carcinoma.

	HGSC	Endometrioid	Mucinous	LGSC
Median age (years)	53	51	57	50.5
FIGO stages				
I	–	16 (55)	8 (89)	3 (21)
II	–	2 (7)	–	2 (14)
III	22 (76)	9 (31)	–	7 (50)
IV	7 (24)	2 (7)	1 (11)	2 (14)
Histological grade				
G1		6 (21)		
G2		18 (62)		
G3		5 (17)		
Debulking				
Optimal <1 cm	20 (67)	24 (83)	8 (89)	14 (100)
Suboptimal >1 cm	9 (33)	5 (17)	1 (11)	–

Absolute values (percentage).
HGSC, high-grade serous carcinoma; LGSC, low grade serous carcinoma.
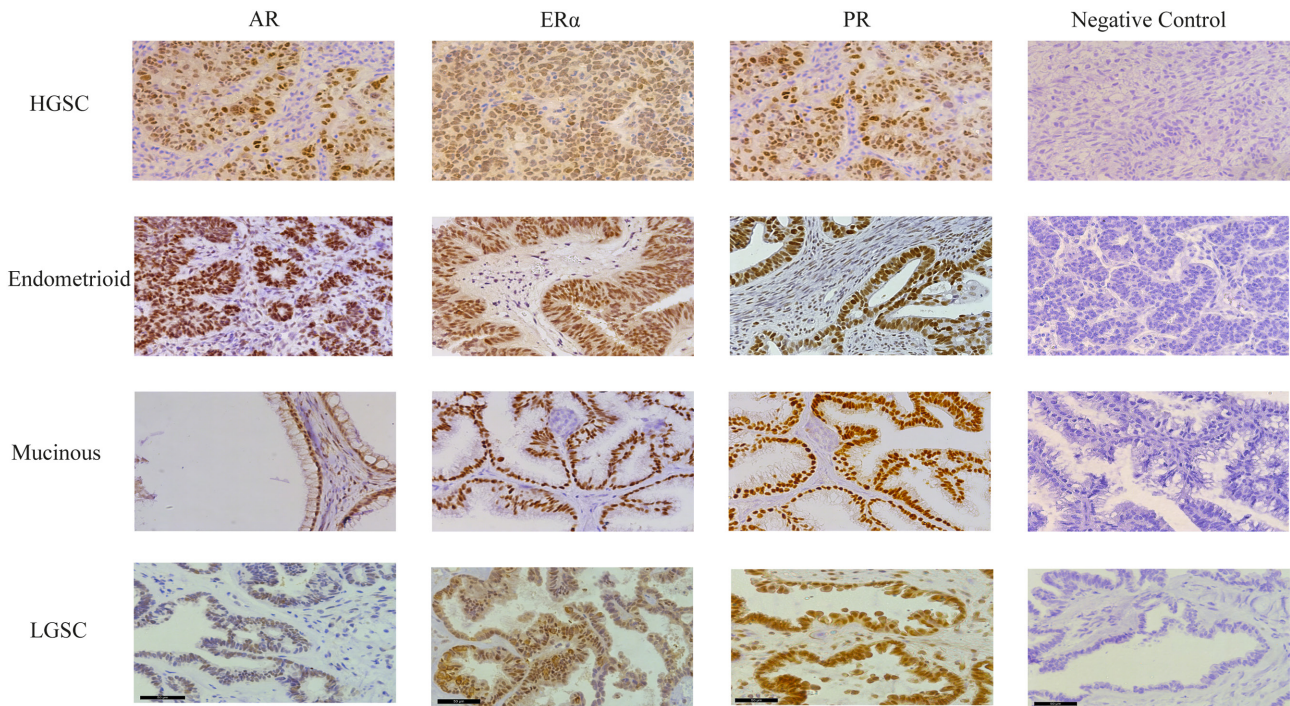
Figure 1

Immunohistochemistry for AR, ER, PR and Ki67 in four histological subtypes of ovarian carcinoma. HGSC, endometrioid, mucinous and LGSC are displayed at the same magnification, bars represent 50 μm.

co-expressed ER with either AR, PR or both; furthermore, the percentage of Ki-67-positive cells was reduced when only ER was expressed vs triple-negative carcinoma. These observations have not been registered in HGSC, probably because only one tumor displayed AR+ ER+ PR+ and another one AR− ER+ PR+ profile; however, the reduction in the proliferation index in HGSC is significant lower when only ER was expressed in comparison to the one observed with only AR (AR+ ER− PR− ($P = 0.05$)).

Discussion

The analysis of the expression of sexual steroid receptors in the distinct histological subtypes of ovarian carcinoma was performed with ovarian tissues collected from a reference oncology hospital in Mexico City. All the tissue samples were processed following the international protocol for tissue banks (26); additionally, the histopathologic diagnosis was supervised by DPM, gynecopathologist of INCAN. Therefore, the comparison observed within the histological subtypes constitutes a reliable result.

The frequency observed for each receptor in the whole population of ovarian carcinoma has been previously described (16, 17, 18); however, variation in the percentage reported for all three receptors are observed comparing the

present and other published works; a possible explanation for this result could be the H30 score considered here for positive data.

The analysis of the receptors expressed in each histological subtype of ovarian carcinoma shows that ER expression in endometrioid carcinoma displays a twofold increase in the proportion compared to the value
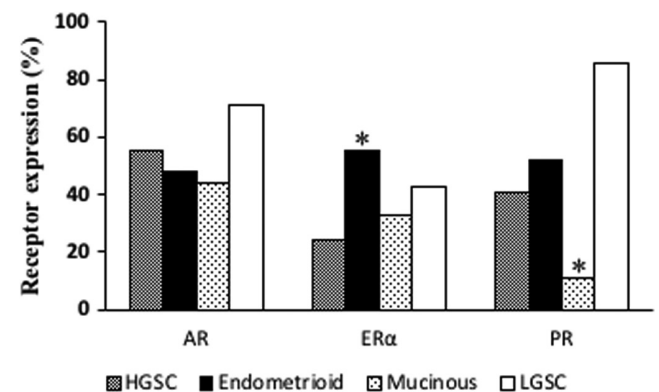

Figure 2

Frequency of immunoreactivity for AR, ER, and PR observed in four histological subtypes of ovarian carcinoma. The presence of AR is similar in all subtypes. Endometrioid carcinoma displayed a higher frequency of ER compared to HGSC. Progesterone receptor is significantly reduced in mucinous carcinoma versus the other three subtypes. Chi square of Pearson, *$P < 0.05$.
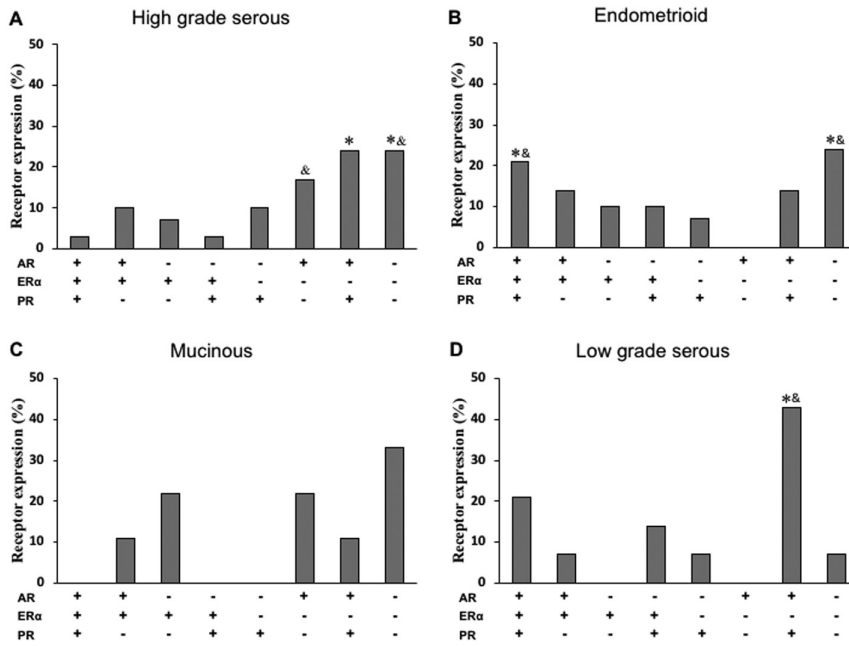
Figure 3

Profiles of steroid receptors in ovarian carcinoma. The frequency of immunoreactivity in eight possible AR, ER, and PR combinations is represented for each histological subtype. Comparison within profiles: (A) HGSC: AR+ER−PR+ and AR−ER−PR−, are more frequent than AR+ER+PR+. (B) Endometrioid: AR+ER+PR+ and AR−ER− PR−, are more frequent than AR+ER−PR−. (C) No significant differences are observed in mucinous carcinoma. (D) LGSC: AR+ER−PR+ predominates over all other combinations but not versus AR+ER+PR+ and AR−ER+PR+ combinations. Analysis of proportions, *$P \leq 0.05$. Comparison within subtypes: AR+ER+PR+ in endometrioid carcinoma is more frequent than the percentages observed in HGSC and mucinous. The frequency of AR+ER−PR+ is higher in LGSC versus endometrioid. The presence of only AR (AR+ ER− PR−) is significantly more frequent in HGSC than in endometroid and LGSC. The frequency of AR−ER−, PR− co-expression in HGSC and endometroid is increased versus LGSC. Analysis of proportions, &indicates $P \leq 0.05$.

observed in HGSC. This difference was not observed when compared to LGSC (Fig. 2). Another observation is the reduced proportion of PR in mucinous carcinoma; at least a fourfold reduction is detected in comparison to the other histological subtypes. These findings are similar to previous reports describing a high frequency of ER in endometrioid carcinoma and a reduced expression of PR in mucinous subtype cases (21, 27, 28).

The description of eight possible combinations of AR, ER and PR in the distinct subtypes of ovarian carcinoma resulted in a profile for each subtype. Although some of the combinations have been previously evaluated (17, 18, 28); to our knowledge, this is the first study to characterize AR, ER and PR combinations in ovarian carcinoma of Mexican women. Worthy of attention and further studies are the reduced proportion of triple positive in HGSC, the absence of AR+ER− PR− combination in LGSC and endometrioid carcinoma and the poor expression of steroid hormone receptors in mucinous carcinoma. Endometrioid carcinoma shows the highest proportion of triple positive receptor and the highest frequency of ER suggesting being a neoplasm responsive to hormones. Additionally, evidence of enzymes involved in steroid hormone metabolism in stromal cells of ovarian carcinoma (29, 30), stresses the probable significance of sexual steroid hormones in the progression of this malignancy.

The reduced proliferation index is observed in the endometrioid subtype when ER is present without co-expression of AR and PR. Interestingly, co-expression of

ER with AR, PR or both does not show a reduction in the proliferation index. The effect generated by the presence of only one receptor differ when it is co-expressed with another receptor, suggesting that receptor crosstalk could play an important role in the pathogenesis of ovarian tumors. The importance of biological crosstalk between steroid receptors has been largely demonstrated in breast cancer (31). Similarly, the proliferation index is significantly lower in only ER-positive tumors than triple-negative ones, supporting previous findings of a better prognosis for ER-positive ovarian carcinoma (32, 33).

On the other hand, a reduction in the proliferation index of ovarian HGSC is observed in only ER positive tumors versus only AR positive; again, the expression of only one receptor shows a significant change. Interestingly,

Table 2 Cell proliferation index of histological subtypes of ovarian carcinoma.

Histological subtype	Mean	s.d.	n	95% confidence interval for mean	
				Lower bound	Upper bound
HGSC	38.0	21.3	29	29.9	46.1
Endometrioid	29.3	14.9	28	23.6	35.1
Mucinous	16.3	14.9	9	4.9	27.7
LGSC	20.2	17.9	14	9.9	30.6
Total	29.4	19.3	80	25.1	33.7

Proliferation index represents the percentage of Ki67 immunolabeled carcinoma cells. Kruskal–Wallis test $P = 0.002$.
HGSC, high-grade serous carcinoma; LGSC, low grade serous carcinoma.

Table 3 Cell proliferation index associated to sexual steroid hormone receptor co-expression in high-grade serous and endometrioid ovarian carcinoma.

Receptors			HGSC			Endometrioid		
AR	ER	PR	Mean	s.d.	*n*	Mean	s.d.	*n*
+	+	+	38.5	–	1	37.5	18.1	5
+	+	–	41.0	18.9	3	30.2	10.1	4
–	+	–	17.6*	21.6	2	8.1*	7.9	3
–	+	+	47.3	–	1	38.7	16.2	3
–	–	+	31.8	28.1	3	41.0	9.8	2
+	–	–	56.4	15.3	5	–	–	–
+	–	+	31.1	16.1	7	21.1	14.2	4
–	–	–	37.3	27.0	7	29.6	9.2	7
Total			38.0	21.3	29	29.3	14.9	28

Proliferation index represents the percentage of Ki67 immunolabeled carcinoma cells. High-grade serous carcinoma (HGSC): Mann–Whitney *U* test *$P<0.05$ of only ER+ vs AR+ ER– PR–. Endometrioid carcinoma: Mann–Whitney *U* test *$P<0.05$ of only ER+ vs AR+ ER+ PR+, AR+ ER+ PR–, AR– ER+ PR+, and vs triple negative tumor.
AR, androgen receptor; ER, estrogen receptor alpha; PR, progesterone receptor.

a previous study have found in HGSC that hazard ratio is significantly different contrasting ovarian tumors that express only ER versus tumors expressing only AR (18). The findings reported in this study, although significant, require the evaluation of a larger cohort of ovarian carcinoma patients to complete and corroborate the relationship of the proliferation index and the presence of steroid hormone receptor combinations.

Ovarian carcinoma subtypes display characteristic profiles of steroid hormone receptors. Evaluation of AR, ER and PR expression and co-expression together with the proliferation index is a non-expensive method that could be routinely applied in ovarian carcinoma patients and associated with the survival rates. The characterization of the steroid hormone profiles in ovarian carcinoma could permit the design of personalized treatments with less aggressive hormonal and anti-hormonal treatments.

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