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The association between androgen receptor expression and some pathological characteristics in patients with breast cancer

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Abstract

Context: Breast cancer is the most current malignancy in women all around the world. Considering the presence of the androgen receptor as a possible prognostic marker, attention has been given to its association with other molecular markers such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her 2)/neu, and clinicopathological characteristics and the target of cancer therapy. **Aims:** This study aimed to assess the level of androgen receptor (AR) and its association with other clinicopathological factors in patients with breast cancer. **Settings and Design:** Samples from 100 breast cancer patients were studied to evaluate the expression of AR using immunohistochemistry. **Subjects and Methods:** The association of AR was evaluated with ER, PR, and Her2 levels; age; tumor size; tumor grade; histological grade; nuclear grade; vascular invasion; perineural invasion; and lymph node involvement. The correlation between the expression of AR and other factors was assessed using *t*, Mann–Whitney, and Chi-square tests using SPSS. **Results:** Among 100 patients, 50 (50%) cases were AR positive. There was a significant correlation between AR expression and triple-negative breast cancer and the expressions of ER, PR, and Her2. However, there was no significant association between AR expression and other clinicopathological markers such as age, tumor size, type of tumor, and histological grade. **Conclusion:** Owning to the expanded expression of AR in 50% of patients with breast cancer in this study as well as the significant association between AR expression and triple-negative breast carcinoma, AR ER, PR, and Her 2, could be considered as a promising prognostic factor.

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Full Text

Introduction

Breast cancer is a common malignancy with the incidence of one million cases a year.[1],[2] It is the second common leading reason behind death following lung cancer in females aged 20–59 years.[3],[4] It is also the leading cause of 16% of all cancers in women and 18.2% of deaths worldwide.[5] It is a probability of 1:8 for a woman to develop breast cancer until the age of 90 years.[6] The incidence of breast cancer increased in developed countries, which seems to be due to the lifestyle and different regimens in women.[5] However, because of the early recognition and favorable treatment of breast carcinoma, the incidence is decreasing.

The diagnosis of breast cancer is done through breast examination, routine mammography, fine-needle aspiration biopsy, and core-needle biopsy.[7] Aspiration cytology is a simple, fast, precise, cheap, and nonaggressive method, which should be evaluated by an expert cytopathologist.[8],[9] Furthermore, aspiration cytology seems to be the best way to diagnose and assess breast lesions.[1],[10],[11]

Breast cancer has several risk factors including age, first relatives with breast cancer, atypical hyperplasia, race, estrogen therapy, radiation, cancer in the cross breast and endometriosis, geographical distribution, food regimen, obesity, sports, and lactation.[11],[12] The prognosis of breast carcinoma is related to several characteristics such as patient's age, early detection, pregnancy, necrosis, tumor size, BRCA1, Her2, p53, estrogen receptor (ER) and progesterone receptor (PR) expression, tumoral emboli to lymphatics, microvessel density, and metastasis to lymph node under the armpit. Several prognostic factors, such as the status of tumor markers at the time of diagnosis, are considered to determine the severity of the disease and choose a treatment modality. These factors can help assess the potential of invasion and the effectiveness of cotreatments such as chemotherapy.[13],[14] Detection of ER, PR, and Her2 as a predictor and prognostic markers in breast cancer can result in advance of targeted therapies such as using tamoxifen, aromatase inhibitors, and trastuzumab. In this line, the detection of novel promising markers such as androgen receptor (AR) seems to be useful in the progress of innovative therapies in breast cancer.[15]

AR is steroid hormone receptors (ligand-activated nuclear transcription factor) that have a similar structure to receptors of progesterone, estrogen, thyroid hormone, glucocorticoid, retinoid, and mineralocorticoid.[16] Three functional parts of AR include the DNA-binding domain and the ligand-binding domain and N-terminal transcription factor.[17] Similar to testosterone and dihydrotestosterone, the activity of androgen is regulated by AR as a member of the nuclear receptor family of steroid hormone. Owning to the expression of AR in a large number of cells and tissues, it plays several functions such as development and protection of reproduction, immune, hematopoietic,muscular skeleton, and cardiovascular systems. The role of androgen is mediated by the pathway dependent on interaction with DNA to regulate transcription of target genes and independent on DNA interaction for the onset of cellular events.[18],[19] The signaling pathways from AR seem to be involved in tumors of prostate, bladder, breast, liver, and kidney.[20] It has been shown that AR is expressed in more than 70% of breast carcinoma, and the AR positivity is considerably high compared with other markers such as ER and PR.[21],[22],[23] Nuclear ARs have different expressions from 80% to 85% in early breast cancer and 60%–75% in metastatic cases. In triple-negative breast cancer (TNBC), the expression of AR is about 53%. Recent clinical studies have shown that some antiandrogenic therapies, including enzalutamide and abiraterone acetate alone and together with other medicines, are useful in treating breast cancer, especially those with focal invasion, or with metastasis, and also in TNBC.[24] The expression of AR is measured using immunohistochemistry. Specimens with 10% or more nuclear staining are considered as AR positive.[25],[26]

AR and its ligand androgens may play a vital role in breast cancer, but the clinical impact of the expression of AR was not well identified. This study aimed to evaluate the level of AR in samples of breast carcinoma and its association with other clinicopathological factors in patients with breast cancer.

Subjects and Methods

Materials

AR, PR, ER, Her2, liquid 3, 3′-diaminobenzidine tetrahydrochloride (DAB)+ Substrate Chromogen System, Envision, Biotin Blocking System, Dual Link System DakoK3468, Denmark); Target Retrieval Solution (DAKO S2367, Denmark); Hematoxylin (Panreac, Spain); Primary and secondary antibody (Master Diagnosis, Spain); Hydrogen peroxide, Methyl alcohol, Entelan glue, Ethyl alcohol 99.6%, NaCl, ethylenediaminetetraacetic acid and Tris (hydroxymethyl) aminomethane (All from Merk, Germany); Ethyl alcohol 96–70% and Xylene (Shiminab, Iran); Pepsin (Sigma, Germany). During the test, all test apparatuses were standard and calibrated.

Patients' samples

Retrospectively, 100 formalin-fixed paraffin-embedded tissues were selected from the patients who had been referred to Imam Reza Hospital, Kermanshah city, Iran. Excision less than total mastectomy includes specimens designated excision, segmental resection, lumpectomy, quadrantectomy, and segmental or partial mastectomy with axillary content. Slides were ready from paraffin blocks of the specimens and stained with the quality standard hematoxylin and eosin (H and E) method. All the specimens were analyzed, and two freelance pathologists confirmed the original diagnoses. The sample size was calculated by the available sampling method and subsequent formula:

[INLINE:1]

In which n = Sample size; [INSIDE:1] Confidence interval, P = Estimated proportion, and d = Desired precision.

Therefore, [INSIDE:2]

The inclusion criteria for the samples were selecting tissue samples of primary breast carcinoma. The exclusion criteria were patients with metastatic breast carcinoma and men with breast cancer. The Ethics Committee of Kermanshah University of Medical Sciences approved the study (code number: KUMS. REC.1394.47) in 2014.

Hematoxylin and eosin staining

4-μm sections of paraffin-embedded tissues were stained with H and E method. The subsequent step is to incubate the glass slides containing tissue sections (70°C for 2 h). Then, the slides were washed in several jars full of xylene, a series of ethanol solutions, hematoxylin, lithium carbonate, and eosin. Two pathologists independently assessed the stained sections.

Immunohistochemistry

Immunohistological staining was carried out on formalin-fixed paraffin-embedded tissue sections using antibodies against AR, PR, ER, and human epidermal growth factor receptor 2 (Her 2). as described previously.[27] For this, 4-μm tissue sections were deparaffinized for 24 h at 60°C–65°C. Afterward, the slides were rehydrated for approximately 45 min in xylene and a graded sequence of ethanol solutions. The slides were immersed in the jar containing Tris buffer (pH = 9) and warmed for 20 min in the autoclave at 121°C followed by washing in PBS solution to retrieve antigens. Then, the slides were soaked for 15 min in a solution of 3% hydrogen peroxide in methanol, washed with phosphate-buffered saline (PBS), to quench peroxidase intracellular activity. Biotin was then applied to improve staining specificity.

After washing with PBS, the slides were incubated by primary and secondary antibodies at 60 and 45 min, respectively, in a humid and dark place at room temperature. The slides were washed in PBS and stained with the substrate–chromogen solution known as DAB for 5 min. The counterstaining was carried out for 30–60 s with hematoxylin then lithium carbonate (5 min) and washed in water. The stained slides were immersed in a graded ethanol series and then xylene to tissue transparency and dehydration. Then, the slides were mounted under a microscope to the test. Negative controls were applied to antibody diluents to remove the primary antibody.

AR-positive samples were stained in more than 10% of tumoral cells; otherwise, they would be classified in the negative group [Figure 1]. If more than 1% of tumor cells had nuclear staining of PR, they were considered positive PR cells. Her2/neu is diagnosed with membrane staining based on complete or incomplete staining and tumor cell staining intensity. Score 0 demonstrates no membrane staining or <10% of the tumor cells, score 1+ reveals mild membrane incomplete staining in more than 10% of the tumor cells, score 2+ presents a weak or moderate complete membrane staining in more than 10% of the tumor cells, and score 3+ shows a robust and complete membrane staining in more than 30% of the tumor cells.{Figure 1}

Statistical analysis

Using (SPSS Inc., Chicago, IL, USA), the data were analyzed using t, Mann–Whitney, and Chi-square measures; the association between the expression of AR and other variables was tested. All

differences were considered statistically significant at the level of $P < 0.05$.

Results

All the participants in this sample are people with early breast cancer. In this study, all the patients were women with early breast carcinoma. One hundred patients in this study had invasive ductal carcinoma, and one case had invasive lobular carcinoma. [Table 1] summarizes the clinicopathological characteristics of the patients. The minimum age of the patients was 19 years, and the maximum period was 78 years, with the mean age of 49 years. The tumor size range was 5–100 mm, an average of 31 mm. Fifty percent of the patients were AR positive, and 50% were AR negative. No significant association was found between the expression of AR and age ($P = 0.343$). According to the Mann–Whitney and Chi-square tests, there was no significant association between the tumor type, tumor size, microscopic grade, and nuclear grade of the tumor with the level of AR expression ($P = 0.568$, 0.109, 0.854, and 0.216, respectively). Furthermore, the Chi-square test indicated that there was no vascular invasion, neural invasion, and lymph node involvement ($P = 0.509$, 0.229, and 0.838, respectively). Evaluation of the expression of AR in TNBC indicated that 29.42% of TNBC were AR positive, and there was a significant association between the level of AR and TNBC [$P = 0.003$, [Table 2]]. Furthermore, the results of Chi-square test showed that there was a significant relationship between the level of AR expression and the level of ER ($P = 0.001$), PR ($P = 0.027$), and Her 2 ($P = 0.029$). AR expression was observed in 56% (28 of 50) of PR-positive and 64% (32 of 50) of ER-positive cancers and 24% (12 of 50) of Her 2-positive cancer patients. AR expression was observed in 44% (22 of 50) of PR-negative and 36% (18 of 50) of ER-negative and 76% (38 of 50) of Her2-positive cancer patients.{Table 1}{Table 2}

Discussion

Breast cancer has a worldwide distribution and is the most common malignancy as one out of eight women is affected by the disease.[1],[2] However, given that several novel therapeutic strategies and diagnostic methods have been developed to detect tumors in early stages (<2 cm), the incidence of death from breast carcinoma has decreased in recent decades.[1],[2] Breast cancer has been suggested to be a common and heterogeneous disorder. In this line, some clinical factors are considered to be important in the determination of prognosis and even treatment, including age, lymph node involvement, tumor size, tumor type, grade, and neural invasion.[28] There is also a wide range of growth and development of breast cancer cells, which affects the clinical period of the disease and is the most critical factor in prognosis.[29]

It is well established that androgen promotes the growth of prostate cancer and estrogen promotes the growth of breast cancer. The effectiveness of androgen for breast cancer therapy, however, has not been well characterized. Conflict findings have been found in research on the role of androgen in breast cancer.[29],[30]

Fujita demonstrated that, in vitro, androgen had an inhibitory effect on breast cancer at normal plasma levels.[31]

Our results showed that half of the studied patients were AR positive. McNamara et al. showed that AR was diagnosed in 85% of early breast cancer patients and 75% of metastatic cases.[32] In a study by Collins et al., the expression of AR in 2171 invasive breast cancers and 246 ductal carcinomas in situ was 77% and 86%, respectively.[33] Hu et al. showed that among 1467 breast cancer cases, 78.7% were AR positive. Of the 1164 ER-positive cases, 88% were AR positive, which was associated with a considerable decrease in death.[34] In 2010, showed that among 652 breast cancer patients with the mean age of 49 years, 72.9% expressed AR, which was higher than the expression of ER and PR.[34] In a cohort study by Anand et al. in India in 2017, the study of AR expression among 116 patients showed no association of AR with age and size of tumors that were in line with our research.[35] Mohammadizadeh et al. showed that 64.3% of breast cancer cases were AR positive that were among the younger population with an increased level of tumors and smaller size (<2 cm). However, the grade and stage of tumor in cases with negative AR were more than patients with positive AR without a substantial difference between the two groups.[36]

Two previous studies have suggested the association of AR-positive status with older age at the time of diagnosis.[37],[38] On the contrary, the research in Iran stated that patients with AR-positive tumors were younger than patients with AR negative. Most research, however, has declared that age does not seem to impact AR positivity.[39],[40]

The present research showed no association between tumor size and AR status. Other studies, however, have indicated that the smaller tumors are more likely to be AR positive.[38],[40] Payandeh et al. reported that there was no statistical correlation between AR and the type of tumor.[41] In another study, the expression of AR was 73.7% in different types of ductal carcinoma. The higher levels of AR

positive were observed in carcinomas of tubular (100%), apocrine (100%), lobular (83.3%), and papillary (81%), whereas the higher levels of AR negative were found in plastic, medullary, and mucinous types.[42] It has been reported that AR is continually expressed in several types of breast cancer, such as apocrine and lobular carcinoma, whereas it is minimally expressed in some other types, including mucinous. However, these studies have been conducted in a small population.[37],[43] The involvement of lymph nodes is one of the important predictive and prognostic factors for outcomes of patients suffering from breast cancer.[44],[45]

We found no statistically significant association between AR expression and involvement of the lymph nodes. Two studies have also verified the lack of significant relationship between expression of AR and involving lymph nodes.[46],[47] Other studies showed a significant association between AR expression and lymph node involvement.[48],[49],[50],[51],[52],[53] The intranuclear receptors, ER and PR, and the membrane receptor Her2 regulate breast cancer growth. ER-positive and PR-positive breast cancers are known to be less aggressive and as sensitive to endocrine care as well. Her2-positive tumors have been identified as aggressive and responsive to trastuzumab and anthracycline therapy.

We found a significant correlation between the expression of AR, ER, PR, and Her 2. Other studies reported that AR was significantly expressed in ER positive and PR positive.[47],[54]

Secreto et al. evaluated ER and AR and they found that 90% of ER-positive tumors were AR positive and also 55% of ER-negative tumors were AR positive.[55]

In another study, 89% of ER-positive breast cancers were AR positive, although only 49% of ER-negative cancers were AR positive.[48]

In this study, we noted that 66% of ER-positive patients and 36% of ER-negative patients expressed AR. We concluded, as with other research, that ER-positive tumors express AR- more than ER-negative tumors.[56]

There were 24% of AR-positive cancers that were HER2 positive and 76% of AR-positive cancers were HER2 negative. We found a significant correlation between HER 2 and AR. Other studies reported that there was no significant association between AR and HER2.[47],[54] Naderi et al. reported a cross action between AR and HER2 in androgen-sensitive tumors.[57]

AR has been found to be expressed in some proportion of TNBC and may play a role in this subgroup as a prognostic marker and a therapeutic target.[23],[58],[59]

In two recent review articles, the AR expression levels in TNBC ranged from 0% to 53%.[37],[51] In this study, 29.42% of TNBC were AR positive, and there was a significant association between the level of AR and TNBC ($P = 0.003$).

Conclusion

Given the well-known prognostic functions of ER, PR, and Her2/neu, detecting the novel, reliable markers is required for effective breast cancer diagnosis and evaluating therapeutic targets. AR could be used as a clinical target due to the presence of AR in 50% of breast cancer patients in this study and its strong interaction with TNBC.

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Conflicts of interest

There are no conflicts of interest.

References

1 Rosai J. Rosai and Ackerman's Surgical Pathology. Amsterdam: Elsevier Health Sciences; 2011.

2 Weidner N, Cote RJ, Suster S, Weiss LM. Modern Surgical Pathology. Amsterdam: Elsevier Health Sciences; 2009.

3 Kamani F, Fathi A. Hormonal receptors evaluation in breast cancer. J Isfahan Med Schl 2011;29.

4 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, *et al*. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71-96.

5 Nordqvist C. Breast cancer: Causes, symptoms and treatments. Med News Today Med Lexicon Intl 2016;5: in press.

6 Walters KA, Simanainen U, Handelsman DJ. Molecular insights into androgen actions in male and female reproductive function from androgen receptor knockout models. Hum Reprod Update 2010;16:543-58.

7 Nazário AC, Facina G, Filassi JR. Breast cancer: News in diagnosis and treatment. Rev Assoc Med Bras (1992) 2015;61:543-52.

8 Gray W, McKee G. Inflammatory Conditions and Benign Breast Lesions. Diagnostic Cytopathology. 2nd ed. London, United Kingdom: Churchill Livingstone; 2003. p. 271-2.

9 Briffod M, Hacène K, Le Doussal V. Immunohistochemistry on cell blocks from fine-needle cytopunctures of primary breast carcinomas and lymph node metastases. Mod Pathol 2000;13:841-50.

10 Carter D. Interpretation of Breast Biopsies. Philadelphia, Pennsylvania, United States: Lippincott Williams & Wilkins; 2003.

11 Ries L, Eisner M, Kosary C, Hankey B, Miller B, Clegg L. Surveillance, Epidemiology, and End Results (SEER) Program SEER* Stat Data base: Incidence-SEER 9 Regs Public-Use, Nov 2004 Sub (1973-2002). National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch. Released April 2005, based on the November 2004 Submission; 2008.

12 Gail MH, Anderson WF, Garcia-Closas M, Sherman ME. Absolute Risk Models for Subtypes of Breast Cancer. Oxford, England: Oxford University Press; 2007.

13 Mylonas I, Makovitzky J, Jeschke U, Briese V, Friese K, Gerber B. Expression of Her2/neu, steroid receptors (ER and PR), Ki67 and p53 in invasive mammary ductal carcinoma associated with ductal carcinoma *in situ* (DCIS) versus invasive breast cancer alone. Anticancer Res 2005;25:1719-23.

14 Hashemi EM, Akbari ME, Najafi M, Haghighat SH, Kaviani A. Role of tumor markers in breast cancer recurrence. Guilan Univ Med Sci J 2006;15:23-8.

15 Safarpour D, Tavassoli FA. A targetable androgen receptor-positive breast cancer subtype hidden among the triple-negative cancers. Arch Pathol Lab Med 2015;139:612-7.

16 Peters AA, Buchanan G, Ricciardelli C, Bianco-Miotto T, Centenera MM, Harris JM, *et al*. Androgen receptor inhibits estrogen receptor-α activity and is prognostic in breast cancer. Cancer Res 2009;69:6131-40.

17 MacLean HE, Warne GL, Zajac JD. Localization of functional domains in the androgen receptor. J Steroid Biochem Mol Biol 1997;62:233-42.

18 Davey RA, Grossmann M. Androgen receptor structure, function and biology: From bench to bedside. Clin Biochem Rev 2016;37:3-15.

19 Yu Q, Niu Y, Liu N, Zhang J, Liu T, Zhang R, *et al*. Expression of androgen receptor in breast cancer and its significance as a prognostic factor. Ann Oncol 2010;22:1288-94.

20 Somboonporn W, Davis SR, National Health and Medical Research Council. Testosterone effects on the breast: Implications for testosterone therapy for women. Endocr Rev 2004;25:374-88.

21 Moinfar F, Okcu M, Tsybrovskyy O, Regitnig P, Lax SF, Weybora W, *et al*. Androgen receptors frequently are expressed in breast carcinomas. Cancer 2003;98:703-11.

22 Kuenen-Boumeester V, Van der Kwast TH, Claassen CC, Look MP, Liem GS, Klijn JG, *et al*. The clinical significance of androgen receptors in breast cancer and their relation to histological and cell biological parameters. Eur J Cancer 1996;32A: 1560-5.

23 Nahleh Z. Androgen receptor as a target for the treatment of hormone receptor-negative breast cancer: An unchartered territory. Future Oncol 2008;4:15-21.

24 Héquet D, Mzoughi S, Rouzier R, Guccione E. Androgen receptors in breast cancer: Expression, value and therapeutic prospects. Bull Cancer 2017;104:363-9.

25 Mishra AK, Agrawal U, Negi S, Bansal A, Mohil R, Chintamani C, *et al*. Expression of androgen receptor in breast cancer & its correlation with other steroid receptors & growth factors. Indian J Med Res 2012;135:843.

26 Zakaria F, El-Mashad N, Mohamed D. Androgen receptor expression as a prognostic and predictive marker in triple-negative breast cancer patients. Alexandria J Med 2016;52:131-40.

27 Danaei S, Madani SH, Khazaei S, Izadi B, Saleh E, Sajadimajd S. The survey of Her2/neu expression and it's correlation with some pathological factors in urothelial bladder tumors. Iran Red Crescent Med J 2018;20:e58494.

28 Cotran R, Kumar V, Robbins S. Pathologic Basis of Disease. Philadelphia, PA: Saunders. Elsevier; 2010.

29 Labrie F, Luu-The V, Labrie C, Bélanger A, Simard J, Lin SX, *et al*. Endocrine and intracrine sources of androgens in women: Inhibition of breast cancer and other roles of androgens and their

precursor dehydroepiandrosterone. Endocr Rev 2003;24:152-82.
30 Wong YC, Xie B. The role of androgens in mammary carcinogenesis. Ital J Anat Embryol 2001;106:111-25.
31 Fujita H. Inhibition and stimulation of proliferation by testosterone in human breast cancer cell MCF-7. Ann Rep Tokyo Metr Inst PH 2004;55:335-8.
32 McNamara KM, Moore NL, Hickey TE, Sasano H, Tilley WD. Complexities of androgen receptor signalling in breast cancer. Endocr Relat Cancer 2014;21:T161-81.
33 Collins LC, Cole KS, Marotti JD, Hu R, Schnitt SJ, Tamimi RM. Androgen receptor expression in breast cancer in relation to molecular phenotype: Results from the nurses' health study. Mod Pathol 2011;24:924-31.
34 Hu R, Dawood S, Holmes MD, Collins LC, Schnitt SJ, Cole K, *et al*. Androgen receptor expression and breast cancer survival in postmenopausal women. Clin Cancer Res 2011;17:1867-74.
35 Anand A, Singh KR, Kumar S, Husain N, Kushwaha JK, Sonkar AA. Androgen receptor expression in an Indian breast cancer cohort with relation to molecular subtypes and response to neoadjuvant chemotherapy-a prospective clinical study. Breast Care 2017;12:160-4.
36 Mohammadizadeh F, Sajadieh S, Sajjadieh H, Kasaei Z. Androgen receptor expression and its relationship with clinicopathological parameters in an Iranian population with invasive breast carcinoma. Adv Biomed Res 2014;3:132.
37 Cho LC, Hsu YH. Expression of androgen, estrogen and progesterone receptors in mucinous carcinoma of the breast. Kaohsiung J Med Sci 2008;24:227-32.
38 Ghannam A, Galal S, Ellity M. Expression of androgen receptors in primary breast cancer. Europ Soc Med Oncol 2016;21:488-92.
39 Mrklić I, Pogorelić Z, Capkun V, Tomić S. Expression of androgen receptors in triple negative breast carcinomas. Acta Histochem 2013;115:344-8.
40 Pistelli M, Caramanti M, Biscotti T, Santinelli A, Pagliacci A, De Lisa M, *et al*. Androgen receptor expression in early triple-negative breast cancer: Clinical significance and prognostic associations. Cancers (Basel) 2014;6:1351-62.
41 Payandeh M, Shazad B, Madani S, Ramezani M, Sadeghi M. Androgen receptor expression and its correlation with other risk factors in triple negative breast cancers: A report from Western Iran. Asian Pac J Cancer Prev 2016;17:3321-4.
42 Park S, Koo J, Park HS, Kim JH, Choi SY, Lee JH, *et al*. Expression of androgen receptors in primary breast cancer. Ann Oncol 2010;21:488-92.
43 Shim HS, Jung WH, Kim H, Park K, Cho NH. Expression of androgen receptors and inhibin/activin α and βA subunits in breast apocrine lesions. APMIS 2006;114:352-8.
44 McGhan LJ, McCullough AE, Protheroe CA, Dueck AC, Lee JJ, Nunez-Nateras R, *et al*. Androgen receptor-positive triple negative breast cancer: A unique breast cancer subtype. Ann Surg Oncol 2014;21:361-7.
45 McNamara KM, Yoda T, Takagi K, Miki Y, Suzuki T, Sasano H. Androgen receptor in triple negative breast cancer. J Steroid Biochem Mol Biol 2013;133:66-76.
46 Choi JE, Kang SH, Lee SJ, Bae YK. Androgen receptor expression predicts decreased survival in early stage triple-negative breast cancer. Ann Surg Oncol 2015;22:82-9.
47 Park S, Koo J, Park H, Kim JH, Choi SY, Lee J, *et al*. Expression of androgen receptors in primary breast cancer. Ann Oncol 2010;21:488-92.
48 Agoff SN, Swanson PE, Linden H, Hawes SE, Lawton TJ. Androgen receptor expression in estrogen receptor-negative breast cancer. Immunohistochemical, clinical, and prognostic associations. Am J Clin Pathol 2003;120:725-31.
49 Bièche I, Parfait B, Tozlu S, Lidereau R, Vidaud M. Quantitation of androgen receptor gene expression in sporadic breast tumors by real-time RT-PCR: Evidence that MYC is an AR-regulated gene. Carcinogenesis 2001;22:1521-6.
50 Isola JJ. Immunohistochemical demonstration of androgen receptor in breast cancer and its relationship to other prognostic factors. J Pathol 1993;170:31-5.
51 Moinfar F, Okcu M, Tsybrovskyy O, Regitnig P, Lax SF, Weybora W, *et al*. Androgen receptors frequently are expressed in breast carcinomas: Potential relevance to new therapeutic strategies. Cancer 2003;98:703-11.
52 Riva C, Dainese E, Caprara G, Rocca PC, Massarelli G, Tot T, *et al*. Immunohistochemical study of androgen receptors in breast carcinoma. Evidence of their frequent expression in lobular carcinoma. Virchows Arch 2005;447:695-700.
53 Søreide JA, Lea OA, Varhaug JE, Skarstein A, Kvinnsland S. Androgen receptors in operable breast cancer: Relation to other steroid hormone receptors, correlations to prognostic factors and predictive value for effect of adjuvant tamoxifen treatment. Eur J Surg Oncol 1992;18:112-8.
54 Ogawa Y, Hai E, Matsumoto K, Ikeda K, Tokunaga S, Nagahara H, *et al*. Androgen receptor expression in breast cancer: Relationship with clinicopathological factors and biomarkers. Int J Clin Oncol 2008;13:431-5.
55 Secreto G, Venturelli E, Meneghini E, Carcangiu ML, Paolini B, Agresti R, *et al*. Androgen receptors and serum testosterone levels identify different subsets of postmenopausal breast cancers. BMC Cancer 2012;12:599.
56 Vojdani R, Geramizadeh B, Mohammadkarimi V, Talei A, Rezvani A, Dorniani G, *et al*. A survey of the relationship between serum testosterone level and expressions of androgen, progesterone and estrogen receptors and HER2 in Iranian women with breast cancer. Middle East J Cancer 2015;6:143-50.
57 Naderi A, Hughes-Davies L. A functionally significant cross-talk between androgen receptor and ErbB2 pathways in estrogen receptor negative breast cancer. Neoplasia 2008;10:542-8.

58 Moe RE, Anderson BO. Androgens and androgen receptors: A clinically neglected sector in breast cancer biology. J Surg Oncol 2007;95:437-9.
59 Rakha EA, El-Sayed ME, Green AR, Lee AH, Robertson JF, Ellis IO. Prognostic markers in triple-negative breast cancer. Cancer 2007;109:25-32.