Breast Cancer (2016) 23:939–944
DOI 10.1007/s12282-015-0661-4

CASE REPORT

A very rare case of breast cancer in a female-to-male transsexual

Yuko Katayama[1] · Takayuki Motoki[3] · Satoko Watanabe[1] · Saiga Miho[1] · Yoshihiro Kimata[1] · Junji Matsuoka[3] · Hiroyoshi Doihara[3] · Yuzaburo Nanba[2]

Received: 28 September 2015 / Accepted: 30 November 2015 / Published online: 11 December 2015
© The Japanese Breast Cancer Society 2015

Abstract The incidence of breast cancer in female-to-male (FTM) transsexuals who received mastectomy and sex reassignment surgery is very rare. In fact, there is only one previous medical report of such a case. We experienced a case of an FTM transsexual who developed breast cancer 12 years after mastectomy and hysterectomy with bilateral salpingo-oophorectomy. Because he had been continuously receiving testosterone during the last 15 years and because histopathological examination revealed positive estrogen receptor and androgen receptor expression, we suggest that exogenous testosterone may have initiated the development of breast cancer via two distinct pathways. We describe the clinical course and condition of the patient and recommend that medical personnel consider the possibility of hormone-related cancer in FTM transsexuals receiving cross-sex hormones.

Keywords Breast cancer · Hormone therapy · Transsexual

✉ Yuko Katayama
u_choppling@yahoo.co.jp

[1] Department of Plastic Surgery, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama-shi, Okayama 700-8558, Japan

[2] Department of Gender Center, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama-shi, Okayama 700-8558, Japan

[3] Department of Breast and Endocrinological Surgery, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama-shi, Okayama 700-8558, Japan

Introduction

Mastectomy and sex reassignment surgery (SRS) allow female-to-male (FTM) transsexuals to live as their desired sex. Androgen administration is also necessary for masculinization. If testosterone-treated FTM transsexuals have had their mammary glands, uterus, and ovaries removed, the future prospect of breast cancer seems unlikely, as breast tissue and estrogen are presumably no longer present. Herein, we present a very rare case of an FTM transsexual who developed breast cancer 12 years after mastectomy and hysterectomy with bilateral salpingo-oophorectomy (BSO). In this case report, we describe his clinical course and discuss this unique clinical condition.

Case report

A 41-year-old FTM transsexual underwent mastectomy and hysterectomy with BSO 12 years ago at our hospital and continuously received testosterone for the last 15 years. He noticed a mass in his left breast and visited his local hospital. As malignancy was suspected, fine-needle aspiration cytology was performed, resulting in a diagnosis of breast cancer. He was referred to our department for treatment and further examination. He gave his informed consent prior to inclusion in this study.

The patient's family history was unremarkable. Mammography of the left breast showed a dense mass with distortion (Fig. 1a). Ultrasonography identified a hypoechoic nodular lesion, approximately 20 mm in size, which was suspected to be malignant (Fig. 1b). Positron emission tomography/computed tomography revealed a lesion with increased uptake in his left breast, but no obvious metastasis (Fig. 1c).

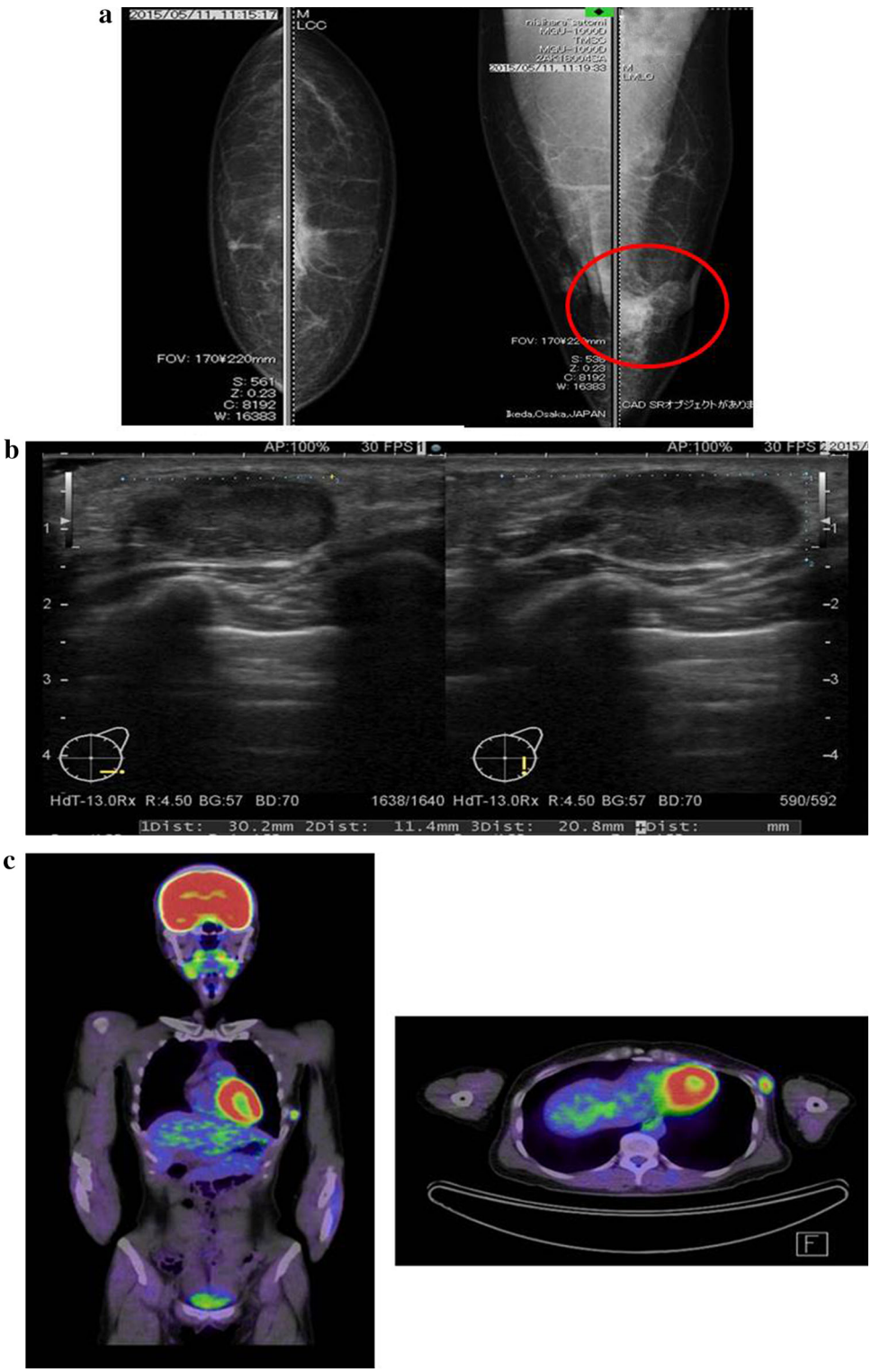

Fig. 1 Preoperative examinations. **a** Mammography showed a high-density mass with distortion. **b** Ultrasonography revealed a hypoechoic nodular lesion of approximately 20 mm. **c** Positron emission tomography/computed tomography revealed a lesion in the left breast. Metastasis was not observed

Subsequently, core needle biopsy was performed. Histopathological examination of the biopsy specimen revealed invasive ductal carcinoma (IDC). Immunohistochemical staining showed the following: estrogen receptor (ER) expression, >50 %; progesterone receptor (PgR) expression, >50 %; human epidermal growth factor receptor 2 (HER-2) expression, negative; and Ki-67 index, 11.4 %. As a result of SRS, the levels of serum follicle-stimulating hormone and luteinizing hormone were elevated (the levels were 131.7 and 38.1 mIU/mL,

respectively). The serum testosterone level was 139.2 ng/dL, owing to androgen administration.

In accordance with the guidelines of the Japanese Breast Cancer Society, the tumor was classified as cT2N0M0, stage IIA. Breast partial resection and sentinel lymph node biopsy were performed under general anesthesia, with surgery beginning with the patient in the supine position. A solid tumor, identified as a palpable mass, was found under his left breast (Fig. 2a). Because the mass was located near the skin, the tumor and surrounding skin were resected en bloc (Fig. 2b). The residual mammary gland, which was near the mass and spreading widely and thinly, was resected as much as possible (Fig. 2c). For the sentinel lymph node biopsy, a small axillary incision was made (Fig. 2b). The operation was successfully completed without any complications.

Histopathological examination of a breast specimen revealed neuroendocrine carcinoma (NEC) (Fig. 3a, b), with no detectable metastasis in the lymph nodes of the left axilla (0/1). ER, PgR, and Ki-67 expression were positive (>50, 1–10, and 20 %, respectively). Androgen receptor (AR) expression was diffusely positive (Fig. 3c), whereas HER-2 expression was negative. The final pathological classification was pT1cN0M0, stage I.

The patient was discharged without any complications after surgery. As follow-up treatments, he received aromatase inhibitors and adjuvant radiation therapy.

Discussion

FTM transsexuals generally receive androgen therapy to achieve masculinity and mastectomy and SRS to live as their desired sex. According to the 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders, the prevalence of FTM transitions ranges from 0.002 to 0.003 % in adults, with a recent report indicating a rate of 5.9 per 100,000 person-years [1].

Numerous transgender patients throughout the world have received androgen therapy and surgical treatments. It is generally assumed that these patients will not develop breast cancer, because they presumably lack breast tissue and estrogen. Nevertheless, breast cancer in testosterone-treated FTM transsexuals has been reported, albeit rarely [1–3]. Other than our case, there is only one reported case of breast cancer in an FTM transsexual receiving testosterone after mastectomy and SRS [4]. The rarity of our case limits discussion of the implications of our novel finding of

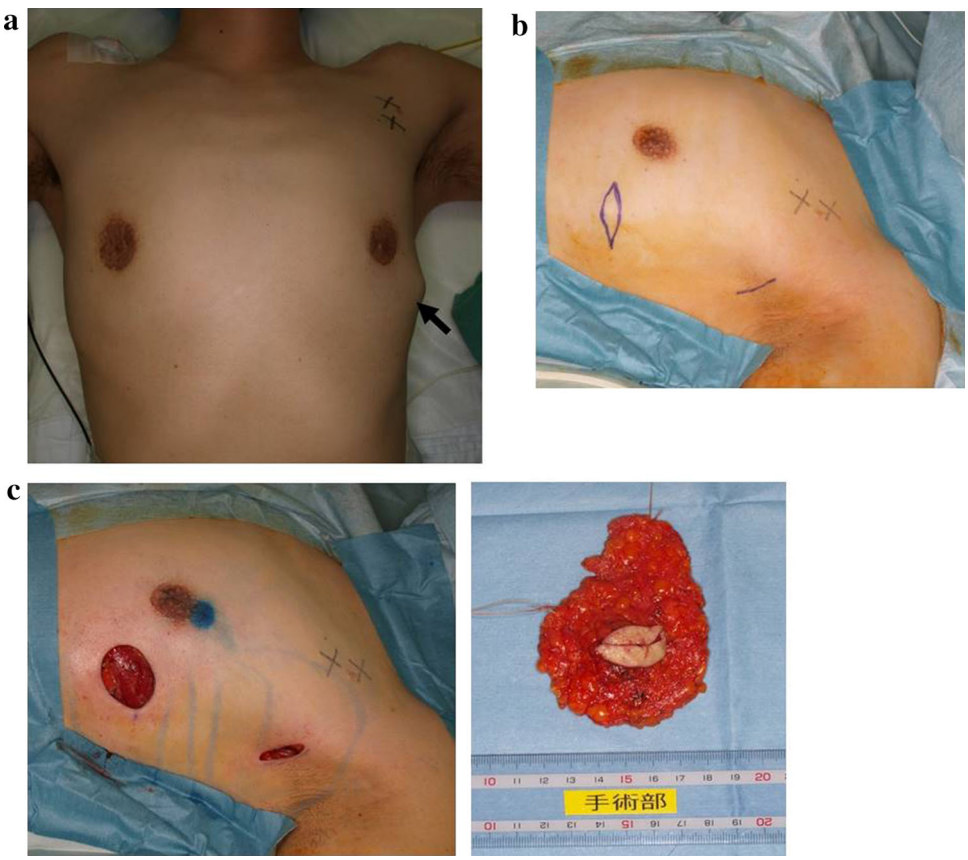

Fig. 2 Intraoperative findings. Breast resection and sentinel lymph node biopsy were performed. **a** A solid tumor was found under the patient's left breast. **b** The tumor was removed along with the surrounding skin, and a small axillary incision was made for sentinel lymph node biopsy. **c** The mammary gland was spread widely and thinly around the mass. The specimen weighed 32 g

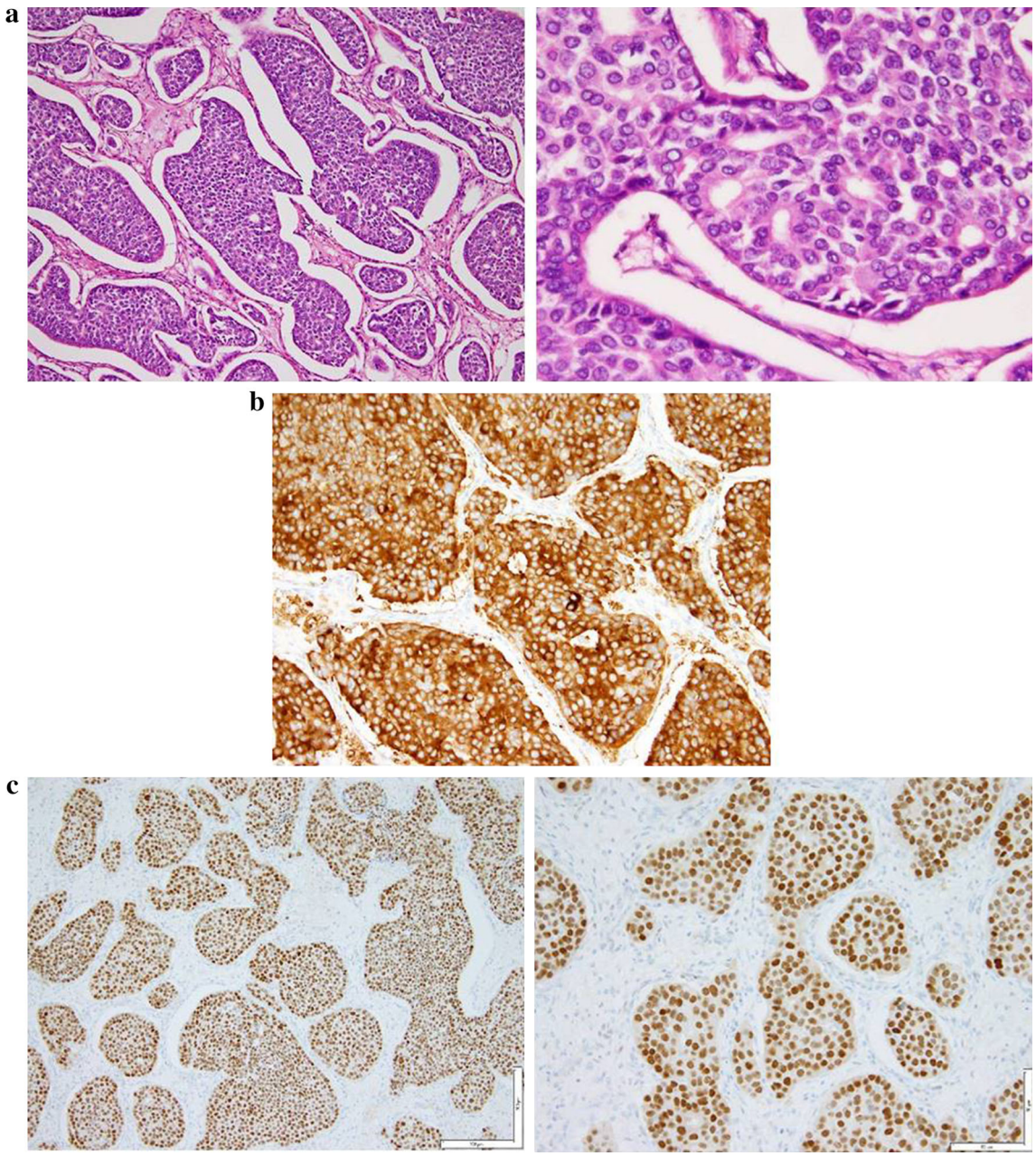

Fig. 3 Histopathological examination. **a** The tumor cells were polarized around the lumina; some cells had eosinophilic granules and a uniform oval nucleus. Hematoxylin–eosin staining. *Left* low magnification; right, *high* magnification. **b** Immunostaining showed diffuse, strongly positive expression of synaptophysin. Staining of chromogranin and cluster of differentiation-56 was negative. High magnification. **c** Staining using an anti-androgen receptor antibody was diffusely positive. *Left* low magnification; *right* high magnification

both ER and AR expression in an FTM patient with breast cancer.

In our case, we suggest that exogenously supplied testosterone stimulated the activity of hormone receptors in residual breast tissue via two different pathways (Fig. 4). In the first, aromatase converts testosterone to estradiol (E2), which stimulates breast cell proliferation by activating ERs. In this pathway, testosterone indirectly stimulates ERs [5, 6]. In the second, 5α-reductase converts testosterone to dihydrotestosterone, which directly affects ARs in AR-positive breast cancer patients [6]. Although ARs are expressed in over 70 % of primary breast cancers (which is comparable to or higher than ER or PgR expression) [7–9], their role in breast cancer remains unclear.

The therapeutic strategy of our case was based on the two pathways mentioned above. Owing to breast partial

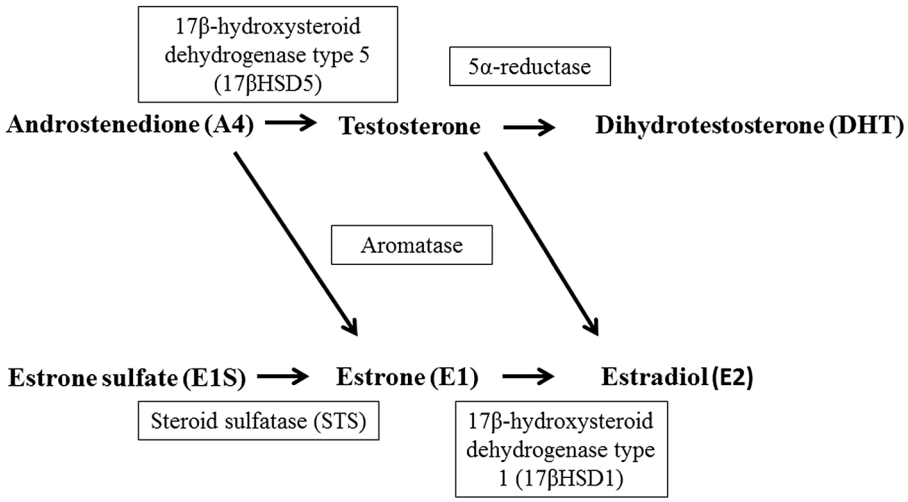

Fig. 4 Estradiol (E2) and dihydrotestosterone (DHT) synthetic pathways. E2 and DHT concentrations are approximately 10 and 3 times higher, respectively, in tumor tissue than in blood, which suggests their local production

resection, radiation therapy was performed. In cases of male breast cancer (MBC), administration of ER modulators such as tamoxifen is also recommended in accordance with the guidelines for treatment of MBC in women [10]. However, we could not use ER modulators in our case because the patient was strongly against feminization. As an alternative, we administered aromatase inhibitors, including anastrozole, to inhibit the conversion of testosterone to E2 (the indirect mechanism).

Regarding testosterone administration, some epidemiological and clinical studies suggest that high levels of circulating androgens increase the risk of developing breast cancer [11, 12], whereas others do not [13, 14]. Therefore, the appropriate therapy for breast cancer and the prognostic value of AR expression in breast cancer are still unclear.

Our case is also interesting because of the histological type of the breast cancer. The patient's breast specimen revealed NEC, which is a relatively rare type of breast cancer with an incidence of approximately 2–5 %. Some reports suggest that NEC has a less favorable prognosis than IDC, which is more common [15]. Because the relationship between our case and NEC is unclear at present, continuous close follow-up of the patient is necessary.

The patient in our case stopped receiving testosterone after surgery. Ideally, endocrine therapy should be discontinued; however, the decision of a patient to resume therapy should be respected and the risk of recurrence clearly explained. In summary, we reported a rare case of an FTM transsexual with breast cancer. We recommend that all medical personnel treating FTM patients bear in mind that breast cancer can develop at any time, even in patients who underwent mastectomy and hysterectomy with BSO.

Acknowledgments We would like to thank Editage (www.editage.jp) for English language editing.

Compliance with ethical standards

Conflict of interest None.

References

1. Gooren L, Bowers M, Lips P, Konings IR. Five new cases of breast cancer in transsexual persons. Andrologia. 2015; 22. doi:10.1111/and.12399.
2. Burcombe RJ, Makris A, Pittam M, Finer N. Breast cancer after bilateral subcutaneous mastectomy in a female-to-male transsexual. Breast. 2003;12:290–3.
3. Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. Clin Breast Cancer. 2011;11:417–9.
4. Dejan V Nikolic, Miroslav L Djordjevic, Miroslav Granic, Aleksandra T Nikolic, Violeta V Stanimirovic, Darko Zdravkovic, et al. Importance of revealing a rare case of breast cancer in a female to male transsexual after bilateral mastectomy. World J Sung Oncol. 2012; 28. doi:10.1186/1477-7819-10-280.
5. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. N Engl J Med. 2006;354:270–82.
6. Secreto G, Zumoff B. Role of androgen excess in the development of estrogen receptor-positive and estrogen receptor-negative breast cancer. Anticancer Res. 2012;32:3223–8.
7. 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.
8. 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.
9. 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.
10. Giordano SH, Buzdar AU, Hortobagyi GN. Breast cancer in men. Ann Intern Med. 2002;15:678–87.
11. James RE, Lukanova A, Dossus L, Becker S, Rinaldi S, Tjonneland A, et al. Postmenopausal serum sex steroids and risk of hormone receptor-positive and -negative breast cancer: a nested case-control study. Cancer Prev Res. 2011;4:1626–35.
12. Nicolas Diaz-Chico B, German Rodriguez F, Gonazalez A, Ramirez R, Bilbao C, Cabrera de Lekon A, et al. Androgens and

androgen receptors in breast cancer. J Steroid Bichem Mol Biol. 2007;105:1–15.
13. Adly L, Hill D, Sherman ME, Sturgeon SR, Fears T, Mies C, et al. Serum concentrations of estrogens, sex hormone-binding globulin, and androgens and risk of breast cancer in postmenopausal women. Int J Cancer. 2006;119:2702–7.
14. Danforth KN, Eliassen AH, Tworoger SS, Missmer SA, Barbieri PL, Rosner BA, et al. The association of plasma androgen levels with breast, ovarian and endometrial cancer risk among postmenopausal women. Int J Cancer. 2010;126:199–207.
15. Wei B, Ding T, Xing Y, Wei W, Tian Z, Tang F, et al. Invasive neuroendocrine carcinoma of the breast: a distinctive subtype of aggressive mammary carcinoma. Cancer. 2010;116:4463–73.