ORIGINAL RESEARCH—ONCOLOGY

Breast Cancer Development in Transsexual Subjects Receiving Cross-Sex Hormone Treatment

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ABSTRACT

Introduction. Transsexual people receive cross-sex hormones as part of their treatment, potentially inducing hormone-sensitive malignancies.

Aim. To examine the occurrence of breast cancer in a large cohort of Dutch male and female transsexual persons, also evaluating whether the epidemiology accords with the natal sex or the new sex.

Main Outcome Measure. Number of people with breast cancer between 1975 and 2011.

Methods. We researched the occurrence of breast cancer among transsexual persons 18–80 years with an exposure to cross-sex hormones between 5 to >30 years. Our study included 2,307 male-to-female (MtF) transsexual persons undergoing androgen deprivation and estrogen administration (52,370 person-years of exposure), and 795 female-to-male (FtM) subjects receiving testosterone (15,974 total years of exposure).

Results. Among MtF individuals one case was encountered, as well as a probable but not proven second case. The estimated rate of 4.1 per 100,000 person-years (95% confidence interval [CI]: 0.8–13.0) was lower than expected if these two cases are regarded as female breast cancer, but within expectations if viewed as male breast cancer. In FtM subjects, who were younger and had shorter exposure to cross-sex hormones compared with the MtF group, one breast cancer case occurred. This translated into a rate of 5.9 per 100,000 person-years (95% CI: 0.5–27.4), again lower than expected for female breast cancer but within expected norms for male breast cancer.

Conclusions. The number of people studied and duration of hormone exposure are limited but it would appear that cross-sex hormone administration does not increase the risk of breast cancer development, in either MtF or FtM transsexual individuals. Breast carcinoma incidences in both groups are comparable to male breast cancers. Cross-sex hormone treatment of transsexual subjects does not seem to be associated with an increased risk of malignant breast development. **Gooren LJ, van Trotsenburg MAA, Giltay EJ, and van Diest PJ. Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. J Sex Med 2013;10:3129–3134.**

Key Words. Breast Cancer Risk; Male-to-Female Transsexual Subject; Female-to-Male Transsexual Subject; Estrogen; Testosterone

Introduction

This study analyzes the occurrence of breast cancer in transsexual people undergoing cross-sex hormone administration. Transsexual people are those with apparently normal somatic sexual differentiation who strongly feel they actually belong to the opposite sex. This conviction is accompanied by an intense desire to live in every way as an ordinary member of the sex that is identified with. Treatment to enable the transition to the opposite sex includes cross-sex hormone administration, usually followed by surgery.

Male-to-Female (MtF) Transsexual Subjects

The induction of female breasts in MtF individuals is of pivotal significance. This requires reduction of androgen impact (since androgens inhibit the formation of female type breast development [1])

Table 1 Breast cancer in male-to-female transsexual subjects, receiving treatment with androgen deprivation and estrogens in the literature

References	Hormone use	Age	Type of breast tumor
1. Symmers, 1968 [6]	Oral contraceptives about 5 years	30 years	Adenocarcinoma + metastases, ER not reported
2. Symmers, 1968 [6]	Unknown	30 years	Intraduct adenocarcinoma + metastases, ER not reported
3. Pritchard et al., 1988 [8]	Estrogens for 10 years	35 years	High grade ductal carcinoma, ER neg
4. Ganly & Taylor, 1995 [9]	14 yrs conjugated estrogens 0.625 mg/day	36 years	Invasive ductal carcinoma, ER neg
5. Grabellus et al., 2005 [10]	Estrogens for about 8 years	46 years	Secretory carcinoma ETV6—NTRK3 gene fusion, ER neg
6. Kelley, 2006 [7]	Unknown but at least 8 years	53 years	Phyllodes, ER neg
7. Dhand & Dhaliwal, 2010 [11]	Estrogens 1969–1978, 1995–1997	58 years	Needle aspiration, ER +, PR +, + metastases
8. Pattison & Mclaren, 2013 [12]	Estrogens since 1995–2002 and 2005–2011	4 years	Invasive ductal carcinoma. ER-, PR- + metastases

ER = estrogen receptor; PR = progesterone receptor; ETV6 = ets variant gene 6; NTRK3 = neurotrophic tyrosine kinase, receptor, type 3

and the establishment of an estrogen environment. A target could be to achieve female androgen levels. There are two studies that have examined the histological features of breast induction in MtF persons, and it has been reported that only in those in whom a progestational anti-androgen (like cyproterone acetate) is combined with feminizing dosages of estrogen therapy will full acinar and lobular formation occur with hormonally stimulated nuclei and pseudolactational changes [2,3]. While androgen-blocking treatment is usually stopped or reduced following surgical procedures including orchidectomy, estrogen treatment has to be continued to prevent the sequels of hormone deprivation such as osteoporosis [4].

One of the concerns of long-term estrogen treatment is the induction of carcinomas of estrogen-sensitive tissues such as the breast [5]. Indeed, eight individual cases of malignancies of the breast in MtF persons have been reported in the literature [6–12] as detailed in Table 1.

Focal apocrine metaplasia was observed in one patient after approximately 54 months of estrogen treatment. In addition, two cases of a fibroadenoma in the breasts of MtF persons have been reported [13,14].

Female-to-Male (FtM) Transsexual Subjects

In testosterone-treated FtM persons there is usually a marked reduction of glandular tissue and an increase of fibrous connective tissue [15,16]. Usually, breasts are surgically removed in the course of sex reassignment treatment, but due to financial constraints this does not always occur. Administered testosterone is partially aromatized to estradiol, and serum estradiol levels do not decrease substantially as a result of testosterone treatment of FtM persons. This can be a risk factor for those who have not undergone mastectomy. The reported cases of breast cancer in FtM individuals are summarized in Table 2. Two cases of breast cancers have been diagnosed in subjects who have been treated with supraphysiological doses of testosterone, suggesting a possible role of testosterone in the development of breast cancer [18], although estradiol derived from aromatization of testosterone may have been relevant as well.

Even those who have undergone mastectomy may still retain some vulnerability and two cases of cancer have been reported in residual breast tissue 10 years after bilateral mastectomy [17,19]. A recent study has also found an association between testosterone administration to FtM transsexual persons and breast cancer–related gene expression signatures [20]. It is not yet clear what the role of testosterone is in the pathogenesis of breast cancer. It may have a role, especially in postmenopausal women [21], though there is no consensus as yet on this topic [22].

Table 2 Breast cancer in female-to-male transsexuals subjects receiving treatment with testosterone in the literature

References	Hormone use	Age	Type of breast tumor
Burcombe et al., 2003 [17]	Testosterone 10 years	33 years	???
Shao et al., 2011 [18]	Testosterone 5 years	53 years	Invasive ductal carcinoma ER+
Shao et al., 2011 [18]	Testosterone 6 years	27 years	Invasive ductal carcinoma ER+
Dejan et al., 2012 [19]	Testosterone 2 ½ years	43 years	Invasive ductal carcinoma

ER = estrogen receptor