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Atypical Ductal Hyperplasia in Men with Gynecomastia: What is Their Breast Cancer Risk?

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Abstract:

Purpose: Atypical ductal hyperplasia (ADH) significantly increases the risk of breast cancer in women. However, little is known about the implications of ADH in men.

Methods: Review of 932 males with breast pathology was performed to identify cases of ADH. Patients were excluded if ADH was upgraded to cancer on excision, or if they had contralateral breast cancer. Cases were reviewed to determine if any male with ADH developed breast cancer.

Results: 19 males were diagnosed with ADH from June 2003-September 2018. All had gynecomastia. Surgical procedure was mastectomy in 8 patients and excision/reduction in 11. One patient had their nipple areola complex removed, and 1 required a free nipple graft.

Median patient age at ADH diagnosis was 25 years (range: 18-72 years). Of the 14 patients with bilateral gynecomastia, 10 had bilateral ADH and 4 had unilateral. 5 cases of ADH were described as severe, bordering on ductal carcinoma in situ. No patient reported a family history of breast cancer. No patient took tamoxifen. At a mean follow-up of 75 months (range: 4-185 months), no patient developed breast cancer.

Conclusion: Our study is the first to provide follow-up information for males with ADH. With 6 years of mean follow-up, no male in our series has developed breast cancer. This suggests that either ADH in men does not pose the same risk as ADH in women or that surgical excision of symptomatic gynecomastia in men effectively reduces the risk of breast cancer.

Key Words: atypical ductal hyperplasia, gynecomastia, male, breast cancer, risk

Background:

Gynecomastia, a benign proliferation of male breast glandular tissue, is not uncommon. It occurs mostly due to an unfavorable balance of estrogen relative to androgen acting on the breast tissue [1]. It is present in 60-90% of neonates, 50-60% of adolescents during puberty, and up to 70% of men over age 50 [1]. Most cases are asymptomatic and self-limited and rarely require work-up and treatment. If the condition persists and causes pain or psychosocial distress, surgery may be offered. If a patient undergoes surgery for gynecomastia, pathologic analysis of the excised tissue is generally recommended to rule out occult breast cancer or other incidental findings [1-3]. The incidence of atypical ductal hyperplasia (ADH) in gynecomastia specimens ranges from 0.4-5.4% [4-6].

It has long been established that women with ADH have an increased risk of breast cancer compared to women of similar ages in the general population [7, 8]. In a prior study by our group of 713 women with ADH not treated with chemoprevention, estimated 5-year and 10-year risks of breast cancer were 4.5% and 17.3%, respectively [9]. Other studies have shown that the 25-year cumulative risk of breast cancer in women with ADH approaches 30% [10, 11]. However, little is known about the implications of finding ADH in men. The purpose of this study was to determine if ADH in men is also associated with an increased breast cancer risk.

Methods:

With Institutional Review Board approval, all electronically available male breast pathology reports from January 1987 to September 2018 from five institutions (Massachusetts General Hospital, Brigham and Womens Hospital, Faulkner Hospital, North Shore Medical Center, and Newton Wellesley Hospital) within Partners Healthcare System Inc., Boston, MA were identified through our large institutional pathology database. Current Procedural Terminology codes for all male breast procedures were also queried to ensure all possible cases of male breast pathology were detected. Pathology reports were

reviewed using natural language processing to identify cases of male ADH [12]. All cases of ADH identified by natural language processing were verified by human readers. Patients were excluded if they had a previous or concurrent (within 6 months) breast cancer diagnosis.

Electronic medical records were reviewed to obtain information regarding patient age at diagnosis, laterality, method of diagnosis (core needle biopsy, excision), extent of surgery, pre-operative imaging, family history of breast cancer, and use of tamoxifen. Subsequent clinician notes and pathology reports were evaluated to determine if any male with ADH developed breast cancer. Length of follow-up signified the time interval from date of diagnosis of ADH to date of last clinician note or date of death.

Results:

Review of 932 male breast pathology reports from January 1987 to September 2018 identified 19 male patients with ADH. There were no documented cases of male ADH prior to June 2003. The other 913 male pathology reports consisted of 120 breast cancers, 4 non-breast cancers, 1 phyllodes tumor, and 788 benign masses or gynecomastia. An additional 42 males underwent cosmetic breast procedures, typically liposuction, in which no tissue was submitted for pathology.

All 19 males diagnosed with ADH had gynecomastia--14 patients had bilateral gynecomastia and 5 patients had unilateral gynecomastia (Table I). Cause of gynecomastia was listed as medication-related in 2, anabolic steroids in 1, alcohol abuse in 1, low testosterone in 1, obesity in 1, possibly trauma in 1, and unknown/idiopathic in 12 patients. Pre-operative imaging included mammography in 7 patients and both mammography and ultrasound in 3 patients; 9 patients had no pre-operative imaging.

Description of surgical procedure was mastectomy in 8 patients and excision or reduction mammoplasty in 11 patients. One patient with severe ADH had their nipple areola complex removed at the time of mastectomy, and 1 patient required a free nipple graft, while the remainder had subcutaneous

mastectomies with excision of most breast tissue except for a small amount under the nipple areola complex.

Median patient age at ADH diagnosis was 25 years (range: 18-72 years). Of the 14 patients with bilateral gynecomastia, 10 had bilateral ADH and 4 were unilateral. 5 cases of ADH were described as severe ADH, bordering on DCIS. No patient received radiation therapy or took tamoxifen. No patient reported a family history of breast cancer. At a mean follow-up of 75 months (range: 4-185 months), no patient developed breast cancer. 1 patient developed recurrence of gynecomastia 2 years after initial surgery and 1 patient developed bloody nipple discharge almost 5 years after initial surgery; both with benign pathology on subsequent excision.

Conclusions:

There are few reported cases of ADH in males with gynecomastia. Most cases are incidentally diagnosed at the time of surgery for gynecomastia. Lapid and colleagues identified 5113 male breasts with gynecomastia in the nationwide network and registry of histopathology and cytopathology in the Netherlands; of these, 18 breasts (0.4%) contained ADH [4]. Koshy and colleagues reviewed the cases of 81 adolescent males who underwent subcutaneous mastectomy for treatment of gynecomastia at three institutions within one healthcare system in Texas, and 1 patient was diagnosed with ADH (1.2%) [5]. In addition, Wells et al identified 17 cases of ADH out of 317 gynecomastia cases (5.4%) at two New York institutions [6]. Through inclusion of additional cases of ADH, Wells was able to report on the findings of 25 total male ADH cases, making it the largest series [6]. In contrast to our study, their main objective was to describe the clinical and histopathologic features of ADH in men with gynecomastia. In their cohort, the mean age at ADH diagnosis was 35 years, which is slightly older than our cohort, but they also noted a distinct peak between 23 and 28 years. In contrast to males, females with ADH are typically

diagnosed later in life, typically in their mid-50s, on the basis of stereotactic biopsy for suspicious microcalcifications identified at the time of screening mammography [13, 14].

We found that half of the patients in our study did not have any pre-operative imaging. According to the American College of Radiology Appropriateness Criteria, males with typical symptoms and physical exam findings of gynecomastia do not require imaging [15]. Typical physical exam findings include a tender, rubbery or firm, mobile mass beneath the nipple areola complex [1]. If clinical exam findings are not typical or indeterminate in males under age 25, ultrasound is recommended and possibly mammography if ultrasound findings are inconclusive [15]. For men age 25 and older with an inconclusive physical exam, mammography is recommended, as it can diagnose gynecomastia and rule out cancer [15]. There are typically three patterns of gynecomastia seen on mammography, including a subareolar nodule (nodular), subareolar flame-shaped tissue (dendritic), and diffuse glandular tissue (similar to a heterogeneously dense woman's breast) [15].

The implication of finding ADH in men with gynecomastia is uncertain. In women with ADH, the estimated 5-year and 10-year risks of breast cancer are 4.5% and 17.3%, respectively [9]. With a mean of 6 years of follow-up, no patient in our series developed breast cancer in either breast. An important limitation of our study is that most of the breast tissue was removed surgically, often on both sides, which likely reduced breast cancer risk similar to women undergoing bilateral prophylactic subcutaneous mastectomy. Also, unlike women with ADH who are screened annually for breast cancer with mammography and often MRI, the men in our study did not have the same rigorous imaging follow-up. In addition, because breast cancer typically occurs in older men, continued follow-up is necessary. Future studies looking at the incidence of ADH in male breast cancer specimens may also help highlight the relationship between ADH and male breast cancer.

In conclusion, our study is the first to provide follow-up information for males with ADH. With 6 years of mean follow-up, no male in our series has developed breast cancer. This suggests that either ADH in men does not pose the same risk as ADH in women or that surgical excision of symptomatic gynecomastia in men effectively reduces the risk of breast cancer.

Compliance with Ethical Standards:

Funding: None

Conflict of Interest: The authors declare that they have no conflict of interest.

Conflict of Interest: Suzanne Coopey declares that she has no conflict of interest. Kinyas Kartal declares that he has no conflict of interest. Clara Li declares that she has no conflict of interest. Adam Yala declares that he has no conflict of interest. Regina Barzilay declares that she has no conflict of interest. Heather Faulkner declares that she has no conflict of interest. Tari King declares that she has no conflict of interest. Francisco Acevedo declares that he has no conflict of interest. Judy Garber declares that she has no conflict of interest. Anthony Guidi declares that he has no conflict of interest. Kevin Hughes declares that he has no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent: Because of the retrospective nature of this study with minimal risk to participants, the need for informed consent was waived by our Institutional Review Board.

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Table I: Patient Characteristics, Work-Up, Surgery

Patient Characteristics (n=19)	
Mean Patient Age	25 years (18-72)
Documented Cause of Gynecomastia	
Unknown/Idiopathic	12
Medication	2
Anabolic Steroids	1
Alcohol Abuse	1

Low Testosterone	1
Obesity	1
Possibly Trauma	1
Laterality of Gynecomastia	
Bilateral	14
Right	3
Left	2
Family History of Breast Cancer	
Yes	0
No	19
Pre-operative Work-Up	
Imaging	
Mammogram	7
Mammogram + Ultrasound	3
None	9
Biopsy	
Fine Needle Aspiration*	1
Core Needle Biopsy	2
None	15
Unknown	1
Surgical Procedure	
Mastectomy	8
Excision/Reduction	11
Nipple Excision	
Yes	1
No	17
Free Nipple Graft	1

*FNA was non-diagnostic