Male breast cancer in the twenty-first century: What's new?

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Male breast cancer is an uncommon disease although the incidence has increased over the past 25 years. As with many other rare "orphan" diseases, male breast cancer is understudied. The rarity of the disease precludes prospective randomized clinical trials. In addition, few researchers and minimal funding have focused on breast cancer in men, but further work is clearly needed to better understand this disease. It shares many similarities with breast cancer in women; yet some clear differences have emerged. In this article, the latest information on the epidemiology, biology, and treatment of male breast cancer is reviewed.

KEY WORDS: Epidemiology, Male breast cancer, Prognosis, Treatment

Introduction

Male breast cancer is an uncommon disease that has been the focus of limited research. Because this disease is rare, no randomized trials have been possible, and only one prospective therapeutic study has been published [1]. Most information on breast cancer in men has been collected from retrospective studies spanning several decades, and treatment recommendations have been extrapolated from results of trials in female patients. Because the incidence of male breast cancer is rising [2], there has been an increasing interest in this disease. In this article, the latest information on the epidemiology, genetics, biologic characteristics, and clinical aspects of male breast cancer is covered.

Epidemiology and Risk Factors

In 2005, an estimated 1,690 new cases of male breast cancer will be diagnosed in the U.S., and 460 men will die as a result of breast cancer [3]. Male breast cancer accounts for only 0.7% of all breast cancer diagnoses [4]. The mean age at diagnosis for men with breast cancer is 67 years, which is 5 years older than the average age at diagnosis for women [2]. As in breast cancer in women,

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breast cancer in men has been increasing; the incidence has climbed 26% over the past 25 years [2]. Yet the overall incidence in the U.S. remains low: approximately one case per 100,000 population per year [5]. The etiology of male breast cancer is unclear, but hormonal levels may play a role in the development of this disease. Testicular abnormalities such as undescended testes, congenital inguinal hernia, orchiectomy, orchitis, and infertility have been consistently associated with elevations in breast cancer risk . Benign breast conditions, including history of breast trauma and nipple discharge, have also been reported to increase risk . Whether gynecomastia is a risk factor for male breast cancer is unclear. Klinefelter's syndrome, in which patients carry XXY chromosomes, may be present in 3%–7% of men with breast cancer, giving males with Klinefelter's syndrome a 50-fold greater risk over the general male population [8,9]. Men with a family history of breast cancer in a female relative have 2.5 times the odds of developing breast cancer [10]. As in women, exposure to chest wall radiation, such as in patients previously treated with mantle radiation for Hodgkin's disease, increases the risk of a subsequent breast cancer [8]. Alcohol use, liver disease, obesity, electromagnetic field radiation, and diet have all been proposed as risk factors, but findings have been inconsistent across studies [15].

Genetics

BRCA1 and *BRCA2* are breast cancer susceptibility genes that are responsible for a proportion of cases of heritable breast cancer. In women, mutations in these genes confer a 40%–70% lifetime risk of breast cancer. Mutations in *BRCA1* and *BRCA2* also increase the risk of affected men developing breast cancer, although not to the same absolute risk as in women (Table I). *BRCA1* mutations have been reported in men with breast cancer, although they do not appear to be a common cause of male breast cancer [16-19]. In series of high-risk families undergoing genetic testing, 10%–16% of men with breast cancer have been reported to have *BRCA1* mutations [17]. In population based series of men with breast cancer unselected by family history, *BRCA1* mutations are much less common; 0%-4% of men with breast cancer harbor this mutation [16,18-20]. Mutations in the *BRCA2* gene are more frequent in males with breast cancer, with 4%-16% of men with breast cancer reported to be mutation carriers in population-based series [18-20]. The highest known prevalence is in Iceland, where a founder mutation is present in 40% of men with breast cancer [21]. Male breast cancer in patients with *BRCA2* mutations tends to present at a younger age and may be associated with a poorer survival [22]. Because of the prevalence of these mutations in male breast cancer patients, genetic counseling and testing should be considered. Other genes have been investigated for a potential role in the etiology of male breast cancer, but none has clearly been associated with an increased risk. Mutations in the androgen receptor gene, *PTEN* (Cowden's syndrome), and mismatch repair genes (*hMLH1*) have been reported in male patients with breast cancer [25]. However, none of these genes has been demonstrated to have a causal association with male breast cancer. Further studies are needed to elucidate their role.

Pathologic Characteristics

Ductal carcinoma in situ comprises approximately 10% of breast cancers in men [2]. The most common growth patterns are papillary and cribriform, and the majority of these tumors are low grade [26]. For invasive carcinomas, the ranges of histologic subtypes for female and male breast cancer are similar, but the relative distributions differ [2]. Data from more than 2,000 male patients in the Surveillance, Epidemiology, and End Results (SEER) cancer registry show that 93.7% of male breast cancers are ductal or unclassified carcinomas, 2.6% are papillary, 1.8% are mucinous, and only 1.5% are lobular [2]. This distribution is in contrast to that seen in female breast cancer, in which almost 12% of cancers are lobular carcinomas. Male breast cancers have high rates of hormone-receptor expression. Approximately 90% of male breast cancers express the estrogen receptor, and 81% express the progesterone receptor [2]. Cancers of the male breast are significantly more likely than cancers of the female breast to express hormone receptors, even after adjustment for tumor stage, grade, and patient age [2]. As in female breast cancer, the rates of hormone-receptor positivity increase with increasing patient age [2]. In contrast, the *her2-neu* proto-oncogene is less likely to be overexpressed in cancers of the male breast [27,28]. While former studies performed before improved standardization of methodology probably overestimated *her2-neu* overexpression, a recent series of 75 patients found that only 5% of male breast cancers overexpressed *her2-neu* [28]. Similarly, Bloom et al. found that only one of 58 male breast cancers overexpressed *her2-neu* and that zero of 58 had gene amplification [27]

The role of the androgen receptor in male breast cancer is unclear. The reported rates of androgen- receptor expression have ranged from 34%–95%, but this receptor has not been associated with breast cancer prognosis [29].

Clinical Features

The most common presenting symptoms in male breast cancer patients are a painless subareolar lump, nipple retraction, and bleeding from the nipple [7,30]. As in women, there is a slight preponderance of left-sided versus right-sided disease [31]. Usually the primary consider-

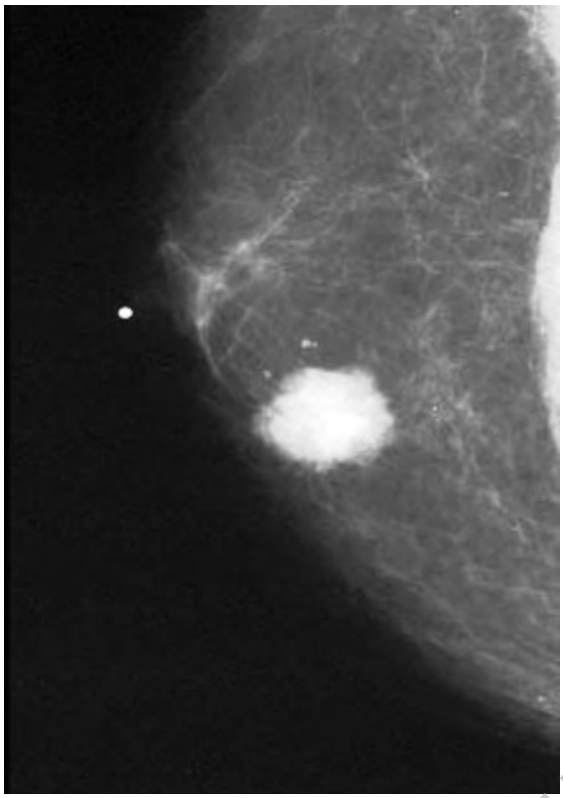

Fig. 1

ation in the differential diagnosis is gynecomastia, which affects approximately 30% of healthy men.
Mammography can be helpful in differentiating gynecomastia from malignant breast disease [58]. An example of a mammogram performed in a male patient with an invasive ductal carcinoma is shown in Fig. 1. Malignant breast tumors are more often eccentric and have irregular spiculated edges. The sensitivity and specificity of mammography for the diagnosis of male breast cancer have been reported to be 92% and 90%, respectively [32]. Ultrasonography can also be a useful adjunct and provide information regarding nodal involvement. After appropriate local imaging, any suspicious mass needs to be biopsied to confirm the diagnosis. Estrogen receptor, progesterone receptor, and *her2-neu* status should be evaluated in every patient, as these may affect the clinical management. The extent of disease can be determined from laboratory evaluation, chest radiography, bone scan, and computed tomography scan of the abdomen, as clinically appropriate. Tumor stage is determined using the American Joint Committee on Cancer classification system, which considers tumor size, nodal involvement, and distant metastases [34]. Tumor size and lymph node involvement are two clear prognostic factors for male patients with breast cancer [2]. Men with tumors measuring 2-5 cm have a 40% higher risk of death than men with tumors <2 cm in maximum diameter [2]. Similarly, men with lymph node involvement have a 50% higher risk of death than those without lymph node involvement [2]. In univariate analyses, negative hormone receptor status and high tumor grade were associated with poorer survival, but these factors do not appear to have independent prognostic value on multivariate analysis [2, 36]. In general, the prognosis for male and female patients with breast cancer is similar 2, 31. Overall survival rates are lower for men, but this is due to an older age at diagnosis and more advanced disease at presentation [2]. When survival is adjusted for age at diagnosis and stage of disease, outcomes are comparable [2]. Disease-specific and overall survival rates by stage of disease for male patients are shown in Table II . Disease-specific survival rates are notably higher than overall survival rates due to the older average age of this population and deaths from other comorbid illnesses.

TABLE I

Study	N. of patients	BRCA1 mutations n (%)	BRCA2 mutations n (%)
Couch et al.	50	–	7 (14)
Thorlacius et al.	30	–	12 (40)
Friedman et al.	54	0	2 (4)
Ottini et al	25	1(4)	4 (16)
Haraldsson et al.	34	–	7 (21)
Kwiatkowska et al.	37	–	4 (11)
Basham et al.	94	0	3 (8)
Sverdlov et al.	31	1 (3)	1 (3)
Frank et al.	76	8 (11)	14 (18)

TABLE II

	Survival rates (%)			
	Stage I	Stage II	Stage III	Stage IV
Disease-specific survival				
3 years	99	93	83	39
5 years	96	88	60	23
10 years	93	74	44	21
Overall survival				
3 years	89	79	66	29
5 years	78	66	39	14
10 years	55	39	21	5

Calculated from SEER database

Treatment of Early-Stage Disease

Local therapy for breast cancer is generally similar in men and women. Most men are treated with modified

TABLE III

No. of patients	SLN biopsy in male breast cancer Cimmino et al.	Port et al.	Goyal et al.	De Cicco et al.	Albo et al.
Total	6	16	9	18	7
SLN identified	6	15	9	18	7
Positive SLN	3	5	5	6	1
Completion ALND	3	4	4	6	1
Additional nodes	1	3	3	1	1
Negative SLN	3	10	4	12	6
Confirmatory ALND	1	6	1	0	3
Additional nodes	0	0	0	n/a	0

Abbreviations: ALND, axillary lymph node dissection; SLN, sentinel lymph node.

radical mastectomy with axillary lymph node dissection or sentinel node biopsy [31]. Historically, radical mastectomy was often performed, but retrospective studies indicate that the outcome for men is equally good when treated with less invasive surgery [37].

Axillary lymphnode dissection is clearly an important component of therapy, because men who have nodal dissection omitted tend to have poorer outcomes [11,38]. For instance, in a series of 397 patients with male breast cancer, 13% of patients without axillary dissection developed regional nodal recurrence compared with 1.2% of patients who underwent axillary dissection [38].

Sentinel node biopsy has been recently evaluated in male patients (Table III) [39-41]. Due to the rarity of this disease, large studies establishing the sensitivity and specificity of sentinel node biopsy in male breast cancer are not possible. However, several case series have been published that have established the feasibility of sentinel node biopsy in the male patient with breast cancer [39-42]. Among a total of 56 male patients combined from these reports, the sentinel node was successfully identified in all but one patient [39-42]. A combined total of 11 patients with a negative sentinel node biopsy underwent confirmatory axillary dissection, and none had any additional nodes [39-42]. This procedure is now being increasingly used in male patients who are clinically node-negative.

There are limited data regarding the indications for adjuvant radiation therapy in male patients, but generally similar guidelines are recommended in men as in women. Men do tend to be treated with radiation therapy more often after mastectomy than women, perhaps because they are more likely to have nipple or skin involvement [31]. Radiation therapy does appear to be effective in preventing local recurrences in male patients, but all studies have been underpowered to address the question of a potential survival benefit [36,38]. To determine which male patients would derive benefit from adjuvant radiation, Perkins et al. studied a series of 142 male patients treated at The University of Texas M. D. Anderson Cancer Center [44]. Overall, 18% of patients experienced locoregional failure, with the most common sites of relapse being the chest wall and supraclavicular areas. Predictors of local regional failure included margin status, tumor size, and the number of involved axillary lymph nodes. Focal skin involvement was not associated with a higher risk of local recurrence.

As for women with breast cancer, adjuvant chemotherapy is used to treat male patients who have a substantial risk of recurrence and death from breast cancer. Whereas the data supporting adjuvant chemotherapy in women are strong [45,57], there is little information on the effectiveness of adjuvant chemotherapy in men. The limited data that have been published, however, do support a similar benefit in male and female patients. One prospective study of adjuvant chemotherapy in men has been published [1]. A series of 24 male patients with stage II breast cancer was treated at the National Cancer Institute with adjuvant CMF (cyclophosphamide, methotrexate, and fluorouracil). The projected 5-year survival rate was >80%, which was significantly higher than a similar cohort of historical controls. Retrospective series have also suggested that adjuvant chemotherapy lowers the risk for recurrence in male patients . Given the established benefit of chemotherapy in women and the suggestive evidence in men, most clinicians use similar guidelines for adjuvant chemotherapy in male and female patients. For instance, at The University of Texas M. D. Anderson Cancer Center, chemotherapy is offered to those patients with breast tumors measuring >1 cm and to those patients with lymph node involvement. Anthracycline-based chemotherapy is offered to those patients without lymph node involvement, whereas both anthracyclines and taxanes are used for those patients with lymph node involvement. An algorithm for the treatment of male breast cancer is illustrated in Fig. 2.

Adjuvant hormonal therapy clearly has a role in male breast cancer patients with hormone receptor–positive tumors [7,35]. Many retrospective series have evaluated the effectiveness of tamoxifen (Nolvadex®; AstraZeneca Pharmaceuticals, Wilmington, DE, http://www.astrazeneca-us.com) in male breast cancer. In the metastatic setting, tamoxifen clearly has activity against male breast cancer [30]. The retrospective series that have evaluated tamoxifen in the adjuvant setting have shown a reduced risk of breast cancer recurrence and death [7,35,46,56]. Given that such a high proportion of males with breast cancer have tumors that express the estrogen or progesterone receptor, most male patients can benefit from adjuvant tamoxifen.

The toxicities of tamoxifen in the male patient have not been extensively studied. One series reported that men had some difficulty tolerating this drug, and side effects, including deep-vein thrombosis, decreased libido, impotence, mood alterations, and hot flashes, have been noted. The role of aromatase inhibitors in the adjuvant setting for male patients is limited. One case series of five patients with metastatic disease treated with aromatase

inhibitors has been published [47]. Of the five patients, three had a period of disease stability, but these patients had indolent disease prior to the addition of an aromatase inhibitor. No patients had objective responses. Anastrozole (Arimidex®; AstraZeneca Pharmaceuticals) has been tested in healthy male volunteers [48]. Men treated with anastrozole did not appear to have as complete estrogen suppression as is seen in women; a 50% decrease in estradiol concentrations was seen. In addition, therapy with anastrozole raised testosterone levels by 58%. However, two recent case reports have described responses in male patients treated with letrozoleb(Femara®; Novartis Pharmaceuticals Corporation, East Hanover, NJ, http://www.pharma.us.novartis.com) [49,50]. Clearly, further investigation is needed to determine the efficacy of aromatase inhibitors in male patients. For now, there are insufficient data to recommend an aromatase inhibitor in the adjuvant setting for male patients.

Treatment of Metastatic Disease

In general, the approach to the treatment of metastatic breast cancer is similar in male and female patients with breast cancer. Given that the vast majority of men have estrogen receptor–positive tumors, hormonal therapy is often the first approach. Farrow and Adair reported on the first male patient to respond to hormonal therapy [51]. They described a male with metastatic breast cancer who had tumor regression after orchiectomy. Although, historically, surgical ablative therapies such as orchiectomy, adrenalectomy, and hypophysectomy have been used effectively to control metastatic breast cancer in male patients, these surgical procedures are rarely used today and have been supplanted by additive hormonal therapies. Tamoxifen has established efficacy in metastatic male breast cancer, with an approximate 50% response rate, and is considered the preferred first-line approach [52].
Luteinizing hormone– releasing hormone agonists, with or without antiandrogens, have also been reported to be effective in male breast cancer. There have been case reports of responses to a wide variety of hormonal therapies including progestins, androgens, steroids, aminoglutethamide, estrogens, and letrozole [49,50,52]. The role of fulvestrant (Faslodex ®; AstraZeneca Pharmaceuticals) remains unclear. For male patients with hormone-refractory disease or rapidly progressing visceral metastases, chemotherapy can provide significant palliation. Generally, a similar approach is used for chemotherapy in metastatic male breast cancer as in female breast cancer. The effectiveness of trastuzumab (Herceptin®; Genentech, Inc., South San Francisco, CA, http://www.gene.com) in *her2-neu* overexpressing male breast cancer is unproven, but certainly seems reasonable given the strong evidence in support of trastuzumab in women with breast cancer.

Second Primaries

Male breast cancer survivors have an increased risk of developing second primary cancers. Data from the Swedish Family-Cancer Database indicate that men with breast cancer have a 93-fold greater risk of developing contralateral breast cancer than men with no history of breast cancer [53]. The absolute risk for an individual male patient developing contralateral breast cancer was 1.75%. Auvinen et al. reported similar findings from the SEER cancer registry database; men with a history of breast cancer had a 30-fold greater risk of contralateral breast cancer [54]. The risk for other cancers, including melanoma and prostate cancer, may also be elevated in male breast cancer survivors, particularly in mutation carriers [54].

Conclusions

Male breast cancer remains a rare disease, although the incidence is increasing. While breast cancer in men is similar to female breast cancer, there are distinct features that should be appreciated. Risk factors include many conditions that could affect hormonal levels, a family history of breast cancer, Klinefelter's syndrome, and a prior history of radiation exposure. *BRCA1* mutations are associated with some cases, but the link between *BRCA2* mutations and male breast cancer is stronger.
Men tend to be diagnosed at an older age than women and with later stage disease. Most of the histologic subtypes that are seen in women are also present in men, except that lobular histology is much rarer.
Tumors of the male breast are more likely to express the estrogen and progesterone receptors and less likely to overexpress *her2- neu* than breast cancers in women. Sentinel node biopsy appears feasible in male patients, but the data regarding this procedure in the male breast are limited.
Chemotherapy and adjuvant radiation should be offered in clinical situations in which these treatments would be deemed appropriate in women. Given the high prevalence of hormone receptor–positive disease, adjuvant hormonal therapy has an important role in the treatment of the male patient. Tamoxifen remains the gold standard of adjuvant hormonal therapies; the data on aromatase inhibitors are sparse, and these drugs should not currently be used in the adjuvant setting.
Future studies with a focus on disease biology are crucial to advance the understanding of male breast cancer and to optimize the care of all male patients.

Riassunto

Il cancro della mammella maschile è patologia rara anche se la sua incidenza è aumentata negli ultimi 25 anni; come alter malattie rare anche questa è poco studiata in

quanto la bassa frequenza ne preclude studi clinici randomizzati. Questa malattia pur condividendo molte analogie con il cancro della mammella femminile presenta anche chiare differenze. Nell'articolo consideriamo le informazioni più recenti circa epidemiologia, biologia e trattamento.

References

1. Bagley CS, Wesley MN, Young RC, et al.: *Adjuvant chemotherapy in males with cancer of the breast.* Am J Clin Oncol, 1987; 10:55-60.

2. Giordano SH, Cohen DS, Buzdar AU, et al.: *Breast carcinoma in men: A population-based study*. Cancer, 2004; 101:51-57.

3. Jemal A, Murray T, Ward E .et al.: *Cancer statistics, 2005*. CA Cancer J Clin, 2005; 55:10-30.

4. Jemal A, Tiwari RC, Murray T et al.: *Cancer statistics, 2004.* CA Cancer J Clin, 2004; 54:8-29.

5. *Surveillance, Epidemiology, and End Results Program*. Available at http://www.seer.cancer.gov. Accessed August 16, 2004.

6. Sasco AJ, Lowenfels AB, Pasker-de Jong P: *EpidemiologY of male breast cancer. A meta-analysis of published case-control studies and discussion of selected aetiological factors*. (Review article) Int J Cancer, 1993; 53:538-49.

7. Goss PE, Reid C, Pintilie M, et al.: *Male breast carcinoma: A review of 229 patients who presented to the Princess Margaret Hospital during 40 years: 1955-1996.* Cancer, 1999; 85:629-39.

8. Harnden DG, Maclean N, Langlands AO: *Carcinoma of the breast and Klinefelter's syndrome*. J Med Genet, 1971; 8:460-61.

9. Hultborn R, Hanson C, Kopf I, et al.: *Prevalence of Klinefelter's syndrome in male breast cancer patients.* Anticancer Res, 1997; 17:429-297.

10. Rosenblatt KA, Thomas DB, McTiernan A et al.: *Breast cancer in men: Aspects of familial aggregation*. J Natl Cancer Inst, 1991; 83:849-54.

11. Weiderpass E, Ye W, Adami HO, et al.: *Breast cancer risk in male alcoholics in Sweden*. Cancer Causes Control, 2001; 12:661-64.

12. Johnson KC, Pan S, Mao Y: *Risk factors for male breast cancer in Canada, 1994-1998.* Eur J Cancer Prev, 2002; 11:253-63.

13. Ewertz M, Holmberg L, Tretli S et al.: *Risk factors for male breast cancer— a case-control study from Scandinavia.* Acta Oncol, 2001; 40:467-71.

14. Pollan M, Gustavsson P, Floderus B: *Breast cancer, occupation, and exposure to electromagnetic fields among Swedish men*. Am J Ind Med, 2001; 39:276-85.

15. Erren TC: *A meta-analysis of epidemiologic studies of electric and magnetic fields and breast cancer in women and men.* Bioelectromagnetics, 2001; (suppl 5):S105–S119.

16. Sverdlov RS, Barshack I, Bar Sade RB, et al:. *Genetic analyses of male breast cancer in Israel*. Genet Test, 2000; 4:313-17.

17. Frank TS, Deffenbaugh AM, Reid JE, et al.: *Clinical characteristics of Individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals*. J Clin Oncol, 2002; 20:1480-490.

18. Basham VM, Lipscombe JM, Ward JM, et al.: *BRCA1 and BRCA2 mutations in a population-based study of male breast cancer*. Breast Cancer Res, 2002; 4:R2.

19. Ottini L, Masala G, D'Amico C, et al.: *BRCA1 and BRCA2 mutation status and tumor characteristics in male breast cancer: A population-based study in Italy*. Cancer Res, 2003; 63:342-47.

20. Friedman LS, Gayther SA, Kurosaki T, et al.: *Mutation analysis of BRCA1 and BRCA2 in a male breast cancer population*. Am J Hum Genet, 1997; 60:313-19.

21. Thorlacius S, Olafsdottir G, Tryggvadottir L, et al.: *A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes.* Nat Genet, 1996; 13:117-19.

22. Kwiatkowska E, Teresiak M, Filas V, et al.: *BRCA2 mutations and androgen receptor expression as independent predictors of outcome of male breast cancer patients*. Clin Cancer Res, 2003; 9:4452-459.

23. Syrjakoski K, Hyytinen ER, Kuukasjarvi T, et al.: *Androgen receptor gene alterations in Finnish male breast cancer*. Breast Cancer Res Treat, 2003; 77:167-70.

24. Fackenthal JD, Marsh DJ, Richardson AL, et al.: *Male breast cancer in Cowden syndrome patients with germline PTEN mutations*. J Med Genet, 2001; 38:159-64.

25. Boyd J, Rhei E, Federici MG, et al.: *Male breast cancer in the hereditary nonpolyposis colorectal cancer syndrome.* Breast Cancer Res Treat, 1999; 53:87-91.

26. Hittmair AP, Lininger RA, Tavassoli FA: *Ductal carcinoma in situ (DCIS) in the male breast: A morphologic study of 84 cases of pure DCIS and 30 cases of DCIS associated with invasive carcinoma. A preliminary report*. Cancer, 1998; 83:2139-149.

27. Bloom KJ, Govil H, Gattuso P, et al.: *Status of HER-2 in male and female breast carcinoma*. Am J Surg, 2001; 182:389-92.

28. Muir D, Kanthan R, Kanthan SC: *Male versus female breast cancers. A population-based comparative immunohistochemical analysis.* Arch Pathol Lab Med, 2003; 127:36-41.

29. Kidwai N, Gong Y, Sun X, et al.: *Expression of androgen receptor and prostate- specific antigen in male breast carcinoma.* Breast Cancer Res, 2004; 6: R18-R23.

30. Giordano SH, Buzdar AU, Hortobagyi GN: *Breast cancer in men*. Ann Intern Med, 2002; 137:678-87.

31. Scott-Conner CE, Jochimsen PR, Menck HR, et al.: *Male breast cancer: Results of the treatments and prognostic factors in 397 cases*. Eur J Cancer, 1995; 31A:1960-964.

39. Albo D, Ames FC, Hunt KK, et al.: *Evaluation of lymph node status in male breast cancer patients: A role for sentinel lymph node biopsy.* Breast Cancer Res Treat, 2003; 77:9-14.

40. Cimmino VM, Degnim AC, Sabel MS, et al.: *Efficacy of sentinel lymph node biopsy in male breast cancer.* J Surg Oncol, 2004; 86:74-77.

41. Goyal A, Horgan K, Kissin M, et al.: *Sentinel lymph node biopsy in male breast cancer patients*. Eur J Surg Oncol, 2004; 30:480-83.

42. Port ER, Fey JV, Cody HS 3rd, et al.: *Sentinel lymph node biopsy in patients with male breast carcinoma*. Cancer, 2001; 91:319-23.

43. De Cicco C, Baio SM, Veronesi P et al.: *Sentinel node biopsy in male breast cancer*. Nucl Med Commun, 2004; 25:139-43.

44. Perkins GH, Middleton LP, Garcia SM, et al.: *Male breast carcinoma: outcomes and predictors of local-regional failure in patients treated without radiation therapy*. Breast Cancer Res Treat, 2002; 76:121.

45. Early Breast Cancer Trialists' Collaborative Group: *Polychemotherapy for early breast cancer: an overview of the randomised trials*. Lancet, 1998; 352:930-42.

46. Giordano SH, Perkins G, Garcia SM, et al.: *Male breast cancer: the M.D. Anderson experience with adjuvant therapy*. Breast Cancer Res Treat, 2003; 82:S42.

47. Giordano SH, Valero V, Buzdar AU et al.: *Efficacy of anastrozole in male breast cancer*. Am J Clin Oncol, 2002; 25:235-37.

48. Mauras N, O'Brien KO, Klein KO, et al.: *Estrogen suppression in males: Metabolic effects*. J Clin Endocrinol Metab, 2000; 85:2370-377.

49. Zabolotny BP, Zalai CV, Meterissian SH.: *Successful use of letrozole in male breast cancer: A case report and review of hormonal therapy for male breast cancer*. J Surg Oncol, 2005; 90:26-30.

50. Italiano A, Largillier R, Marcy PY et al.: *Complete remission obtained with letrozole in a man with metastatic breast cancer*. Rev Med Interne, 2004; 25:323-24. (French.)

51. Farrow J, Adair F: *Effect of Orchiectomy on skeletal metastases from cancer of the male breast*. Science, 1942; 95:654.

52. Jaiyesimi IA, Buzdar AU, Sahin AA, et al.: *Carcinoma of the male breast*. Breast Cancer Res, 1992; 117:771-77.

53. Dong C, Hemminki K: *Second primary breast cancer in men*. Breast Cancer Res Treat, 2001; 66:171-72.

54. Auvinen A, Curtis RE, Ron E: *Risk of subsequent cancer following breast cancer in men*. J Natl Cancer Inst, 2002; 94:1330-332.

55. Kwiatkowska E, Teresiak M, Lamperska KM, et al.: *BRCA2 germline mutations in male breast cancer patients in the Polish population*. Hum Mutat, 2001; 17:73.

56. Sperlongano P, Pisaniello D: *Current management of male breast cancer*. Ann Ital Chir, 2000; 81:165-66.

57. Privitera A, Ellul E, Giordmaina R, Caruana M, Klauman M, Felice G: *Male Breast cancer: Report of 2 cases and review of the literature*. Ann Ital Chir, 2004, LXXV, 6:669-72.

58. Rubino A, Fissi S, Secreto G: *Bilateral breast cancer in a male with hepatocellular carcinoma. A case report*. Ann Ital Chir, 2008; 79:117-19.