Male breast cancer and female breast cancer: A population-based study

Nan Yao
Aerospace Center Hospital
Wenzai Shi
Peking University International Hospital
Tong Liu
Beijing Shijitan Hospital
Sarah Tan Siyin
Capital Medical University
Weiqi Wang
Aerospace Center Hospital
Ning Duan
Aerospace Center Hospital
Guoshuai Xu
Aerospace Center Hospital
Jun Qu (qujunchief@163.com)
Aerospace Center Hospital

Research Article

Keywords: Male breast cancer, Epidemiology, Prognosis, primary site location

Posted Date: May 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-543446/v1

Abstract

Male breast cancer (MBC) is a rare disease. Due to limited information, MBC has always been understudied. We conducted a retrospective population-based cohort study by using the 2010–2014 Surveillance, Epidemiology, and End Results (SEER) program data. The clinical and biological features of female breast cancer (FBC) patients were compared with MBC patients. Survival curves were constructed with the Kaplan-Meier method. Multivariate Cox regression models and competitive risk models were separately built to identify factors associated with survival time in the MBC and FBC group. Our retrospective study showed that MBC patients suffered with higher TNM stages, higher grades, and more percent of hormone receptor–positive tumors, compared with FBC patients. In addition, the site of the primary breast cancer varied greatly different between genders. FBC patients demonstrated superior overall survival than MBC patients on Kaplan-Meier analysis. In multivariate COX analysis for FBC patients, older age, black race, higher T, N, M-stages, higher grades, estrogen receptor (ER)/progesterone receptor (PR) negative and human epidermal growth factor receptor 2 (HER2) negative were associated with higher risk of death. MBC patients had similar independent prognostic factors, but PR and HER-2 status did not appear to independently influence survival. Interestingly, primary site location was an independent prognostic factor for both MBC patients and FBC patients, which should be considered by clinicians as a prognostic factor.

Introduction:

Breast cancer is one of the most common malignant tumors, and the leading cause of cancer related death in women worldwide. In 2018, there were an estimated 2.1 million new cases of breast cancer and 627,000 deaths from breast cancer worldwide [1]. However, though it is rare, breast cancer in men accounts for 1% of all breast cancer cases [2,3].

Given the low incidence, previous studies on male breast cancer (MBC) have suffered from small sample sizes, short follow-up time, limiting their interpretability. And the therapeutic strategies for MBC patients are commonly extrapolated from those used to treat female breast cancer (FBC) patients[4,5]. No existing evidence-based data support this female-to-male extrapolation. Literatures have suggested that MBC has biological differences compared with FBC. MBC patients is typically associated with advanced stages, higher grades, higher prevalence of hormone receptor–positive, and a worse prognosis [6–11]. Furthermore, studies have proposed MBC patients were insensitivity for adjuvant therapy, not only that, there was an underutilization of therapy in MBC patients compared with FBC patients [12–14]. Therefore, it may be improper to adopt the clinical applications of female-to-male extrapolation.

In the current study, we attempt to compare the clinicopathologic characteristics and prognosis between MBC patients and FBC patients by drawing data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Database from 2010 to 2014. And the aim is to better understand the gender differences and specificity of MBC.

Materials And Methods:

This is a retrospective cohort study of breast cancer patients diagnosed in the SEER database 8.3.4 between 2010 and 2014. SEER collects cancer incidence data from population-based cancer registries covering approximately 34.6% of the U.S. population. It also records data of patients' clinicopathological characteristics, and vital status during follow-up. Breast cancer cases were diagnosed according to the 3rd edition of the International Classification of Diseases for Oncology (ICD-O-3) between 2010 and 2014 via eligibility screening process.

A total of 313,504 patients with breast cancer were identified in the SEER database. Patients were excluded if they had 1) survival month that was 0 or unknown; 2) T0 local disease diagnosis; 3) other malignant tumors. 222,120 patients (1,592 males and 220,528 females) remained in the final analysis (Fig. 1). Demographic and tumor characteristics that was collected include sex, age at diagnosis, laterality (left, right, bilateral), primary site location, race (white, black, and other/unknown), pathological type (ductal, lobular, and other/unknown), TNM stage, histological grade (well differentiated, moderately differentiated, poorly differentiated and anaplastic), surgical situation, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2). Patients who received any type of surgical resection of the primary tumor was considered as having had surgery. For all demographic and tumor characteristics, missing or unknown data were designated as "unknown" for descriptive purposes. Informed consent was obtained from all participants

Statistical Analysis

All statistical analyses were performed using SAS statistical software (version 9.4). The chi-square test was used to compare the distribution of demographic characteristics between male and female patients. Kaplan-Meier survival curves were generated to compare differences in survival probabilities over time between groups, and the equality of these curves was tested using a log-rank statistic.

The interval from the date of cancer diagnosis, to the endpoint was calculated as survival time (months). The endpoint was classified as one of the three events, whichever occurred first: date of breast cancer-related death, date of non-breast cancer related death, or the date used as cutoff for the study. Vital status was classified as dead or alive in the SEER database.

Cox regression models were generated to describe the relationship between clinicopathologic features and risk of breast cancer-related death among MBC patients and FBC patients while controlling for confounders including age, race, pathological type, primary site location, TNM stages, histological grade, surgical situation, ER, PR, and HER-2.

Non-breast cancer related death may occur prior to the occurrence of breast cancer-related death during the follow up period. The traditional multivariate COX regression model may markedly overestimate the absolute risk of the event of interest. To avoid overestimate and to improve accuracy, the cause-specific hazard model (CS model) and sub-distribution hazard function model (SD model) were used to calculate

the absolute risk of breast cancer related death. A two-sided *p*-value < 0.05 was considered statistically significant in this study.

Results:

MBC (n = 1592/222120) represented 0.72% of all breast cancers. The common descriptive characteristics of both genders are presented in Table .

The median age at diagnosis for MBC was 65 years (range, 26–85 + years) compared with 60 years (range, 2–85 + years) for FBC ($p < 0.001$). In MBC patients, the race of patients was predominantly white (80.0%), with 15.1% black and 4.9% other races. In FBC patients, 78.9% were white, 11.5% were black and 9.6% were of others races ($p < 0.001$). Laterality (distribution of breast cancer between right and left breast) also differed significantly between men and women, but there was a slight tendency for left breast predominance in both genders noted in our data ($p < 0.05$). In our study, there were significant differences noted for tumor size($p < 0.001$), lymph node status ($p < 0.001$) and distant metastasis ($p < 0.001$) between men and women. MBC patients were also more likely to present with advanced grades ($p < 0.001$). In terms of pathological types, 81.5% of MBC patients were invasive ductal carcinoma compared with 75.0% in FBC patients. Lobular carcinomas accounted for only 0.7% of breast cancer in MBC patients by the contract of 8.5% in FBC patients ($p < 0.001$). Compared with FBC patients, MBC patients was more likely to express hormone receptor positive. 91.30% of men and 79.3% of women had ER positive tumor ($p < 0.001$). Similarly, MBC patients was more likely to have PR positive tumors than FBC patients (84.5% vs. 68.8%, $p < 0.001$). Compared with FBC patients, MBC patients exhibited lower HER-2 expression (11.2% vs. 14.5%, $p < 0.001$).

Among MBC patients, there were 38.0% of tumors located with central portion, followed by 12.4% in the upper-outer quadrant, 3.6% in the upper-inner quadrant, 1.8% in lower-inner quadrant, 4.0% in lower-outer quadrant (4.0%), 5.3% in nipple, 0.1% in axillary tail, and 22.4% remaining classified as overlapping lesion. However, in FBC patients, there were only 4.6% tumors located in central portion, tumor primarily located in upper-outer, which account for 33.6%. The rest located in the upper-inner quadrant (11.9%), lower-inner quadrant (5.5%), lower-outer quadrant (7.2%), nipple (0.4%), axillary tail (0.5%), and overlapping lesion (15.2%).

During the entire study period, 242 male patients and 23,953 female patients died from breast cancer. The median follow-up was 57 months (range, 1–95 months). The Kaplan-Meier method showed that the MBC patients had a worse overall survival (OS) than FBC patients. The log-rank test showed a significant difference in the OS between the two groups (log-rank, $p < 0.001$, Fig. 2).

Multivariate Cox regression models were generated to describe the association between clinicopathological characteristics and risk of death. Among FBC patients, results indicated that black race, elder age, larger tumor size, higher lymph node involvement, distant metastasis, type of lobular, and higher tumor grade were associated with a higher risk of death. On the contrary, ER positive ($p < 0.001$), PR positive ($p < 0.001$), HER-2 positive ($p < 0.001$) were associated with a significantly lower risk of death.

Additionally, females who underwent surgery had a 65% reduced risk of breast cancer-related death compared with patients who did not receive surgery ($p < 0.001$) (Table). Similar with FBC patients, age, race, pathological type, TNM stages, histological grade, surgical history, and ER were also prognostic factors among MBC patients, but PR and HER-2 status did not appear to independently influence survival (Table). It is worth noting that the primary site location was an independent prognostic factor for both MBC and FBC patients. Internal location tumor was associated with a poorer prognosis compared with lateral location tumor.

12,707 non-breast cancer related death cases were observed before the occurrence of breast cancer related death. Table and summarizes crude and adjusted HRs (95%CI) for the association of clinicopathological characteristics with breast cancer related death after taking competing risk events (none-breast cancer related death) into consideration. No significant differences have been observed between multivariate Cox regression and the competing risk analysis after adjustments were made for the same confounders.

Discussion:

This large-scale population-based study, which makes comparisons between MBC and FBC patients, provides intriguing etiologic and prognostic clues to this disease. Several significant conclusions were made. First, MBC patients has a worse prognosis than FBC patients. Second, the independent prognostic factors between MBC and FBC patients were incompletely same, PR and HER-2 were independent prognostic factors for FBC patients, but not for MBC patients. Finally, breast tumor location between the two genders were different, which might have an important influence on prognostic results.

In our analysis, we have demonstrated that MBC patients has a worse overall prognosis than FBC counterparties. Previous studies agree with our finding. Nahleh et al. found that FBC patients had a significantly longer OS than MBC patients. The median OS for MBC patients was 7.0 years compared with 9.8 years for FBC patients (log-rank test; $p < 0.05$) [9]. Similarly, a study including 2,537 MBC patients also demonstrated that MBC patients had a shorter relative a 5-year survival rate than FBC patients [4]. Several explanations may help to explain this phenomenon. Better prognosis in FBC patients is partly due to the introduction of screening, public awareness, diagnosis at an earlier age with less complications, accurate clinical TNM staging, advances in treatment, and standardization of treatment regimens in international guidelines. However, the situation in MBC patients is differed a lot compared with female counterparts. Firstly, MBC patients tend to be older and are more likely to be afflicted with other chronic diseases including hypertension, coronary heart disease, diabetes and so on, thus affects the prognosis, they also suffer from higher prevalence of advanced breast cancer at presentation, this may reflect a general lack of public awareness about MBC. Secondly, the breast tissue in men is sparser. A small tumor can invade the breast skin rapidly. The tumor can be easily drained into the subareolar lymphatic plexus and thus could lead to a high propensity to metastasize[15]. Third, the prevalence of adjuvant therapies for MBC patients are far behind from FBC patients. A recent analysis of the SEER data from 1996 to 2005 demonstrated that there is a 42% decrease in breast cancer-specific mortality among women compared

with only a 28% decrease among men, suggesting that the treatments being used in MBC patients are not as effective as they are for FBC patients[10]. Furthermore, the use of adjuvant therapy in MBC patients is not widespread as FBC patients. In a paper which included 10,173 men with HR-positive breast cancer, men were less likely to receive adjuvant endocrine therapy than women (67.3% vs 78.9%, $p < 0.001$) [16]. Reliable and widespread use of adjuvant chemotherapy and radiotherapy for men is also lacking[17–20] .

There maybe different risk factors between FBG and MBG especially when it related to PR and HER-2. Likewise, a population-based study indicated PR status did not appear to independently influence survival among MBC patient[4]. Matthew J's study also demonstrated PR status did not affect survival in MBC patients [21]. This may be related to the fact that PR status is not a crucial factor for endocrine therapy, and MBC patients are not as sensitive towards endocrine therapy. Little data are available on HER-2 expression in men. The effectiveness of trastuzumab in HER-2 overexpressing male breast cancer is unproven [22]. In addition, MBC patients with HER-2 positive only comprise of a small portion of all MBC population[23,24], making it difficult to draw a reliable conclusion.

In this current study, the primary location of tumor between the MBC and FBC patients were markedly different. In FBC patients, tumor primarily located in upper-outer, account for 33.6%, other sites in the breast were discovered at lower frequencies, which agrees with previous studies [25–28]. This basic observation has become a common sense, but lack an adequate scientific explanation for this asymmetric occurrence of breast cancer. A possible explanation was the upper-outer quadrant of the breast contains a greater proportion of the epithelial tissue, which had a great chance to occur cancer [29]. In MBC patients, central position (nipple and central portion) is dominate which accounted for half percent (43.3%). The upper-outer quadrant only made up 12.4%, which was far below the central position. This discrepancy may cause by the anatomy of male breast, as there is a larger volume of epithelial breast tissue in the central portion in men[29]. In addition, the prognostic role of the tumor location is also under appreciated, as almost all breast cancer guidelines do not include tumor location as a prognostic factor[30,31]. Yet in our study, tumor location affected the prognosis for both MBC and FBC patients, tumors situated in the internal quadrants of the breast have a worse prognosis compared with those located in lateral quadrants. This finding was compatible with other papers. A paper from David K have suggested that internal tumor location adversely impacts breast cancer–specific survival and OS in breast cancer patients [32]. Similarly, the Caroline trials indicated that internal location was associated with a 50% excess risk of systemic relapse and breast cancer death compared with lateral tumors [33].

The poor prognosis of tumor with internal location may be associated with internal mammary nodes (IMN), which were not conventional treated. Patients with negative and positive axillary lymph node have positive IMN rates ranging from 8–13.7% and 28–48% respectively, as indicated by extensive radical mastectomy data[34–37]. And even there were 5% of breast cancer patients metastasis to IMNs alone [38]. These metastasis IMNs, which is more often involved in internal quadrants, are usually clinically silent and might disseminate the disease, thus affects the prognosis of these patients [39].

The strength of this current study is the large quantity of data regarding MBC and FBC patients, which allows for a reliable extrapolation of results. Furthermore, we analyzed the tumor location within the breast, which has been rarely focused on. Moreover, competing risk regressions were further used to validate our results, increasing the accuracy of the study. However, the main limitations of this study were its missing data, especially on antigen identified by monoclonal antibody Ki-67 status, disease free survival and adjuvant therapy information. The pathologic information was collected from different hospitals and failed to undergo a centralized review. In addition, because of the special status of the disease, the number of MBC and FBC patients were very asymmetric.

Conclusions:

Our retrospective study showed that MBC has a worse overall prognosis than FBC and the independent prognostic factors between MBC and FBC were incompletely the same. In addition, there are such vast differences between genders for tumor location, which should be considered by clinicians as a prognostic factor. MBC should be considered as an independent disease. Future research on MBC is needed in many aspects, including molecular pathology, risk factors, genetic contributions diagnostic and therapeutic tools.

Abbreviations

MBC Male breast cancer

FBC Female breast cancer

ER Estrogen receptor

PR Progesterone receptor

HER2 Human epidermal growth factor receptor 2

OS Overall survival

SEER Surveillance, Epidemiology, and End Results

IMN internal mammary nodes

Declarations

Acknowledgements

Not applicable.

Authors' contributions

Nan Yao and Wenzai Shi executed the study and drafted the manuscript. Nan Yao, Sarah Tan Siyin and Tong Liu participated in the study design and performed the statistical analyses. Weiqi Wang, Ning Duan and Guoshuai Xu contributed to the discussion. Jun Qu reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Aerospace Center Hospital and was complied with the Declaration of Helsinki. The work has been reported in line with the STROCSS criteria and in its references.

References

1 Bray, F. *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians***68**, 394-424, doi:10.3322/caac.21492 (2018).

2 Siegel, R., Naishadham, D. & Jemal, A. Cancer statistics, 2012. *CA: a cancer journal for clinicians***62**, 10-29, doi:10.3322/caac.20138 (2012).

3 Fentiman, I. S., Fourquet, A. & Hortobagyi, G. N. Male breast cancer. *Lancet (London, England)***367**, 595-604, doi:10.1016/s0140-6736(06)68226-3 (2006).

4 Giordano, S. H., Cohen, D. S., Buzdar, A. U., Perkins, G. & Hortobagyi, G. N. Breast carcinoma in men: a population-based study. *Cancer***101**, 51-57, doi:10.1002/cncr.20312 (2004).

5 English, J. C., 3rd, Middleton, C., Patterson, J. W. & Slingluff, C. L. Cancer of the male breast. *International journal of dermatology***39**, 881-886, doi:10.1046/j.1365-4362.2000.00007.x (2000).

6 Yu, X. F., Yang, H. J., Yu, Y., Zou, D. H. & Miao, L. L. A Prognostic Analysis of Male Breast Cancer (MBC) Compared with Post-Menopausal Female Breast Cancer (FBC). *PloS one***10**, e0136670, doi:10.1371/journal.pone.0136670 (2015).

7 Pant, K. & Dutta, U. Understanding and management of male breast cancer: a critical review. *Medical oncology (Northwood, London, England)***25**, 294-298, doi:10.1007/s12032-007-9034-y (2008).

8 Kornegoor, R. *et al.* Molecular subtyping of male breast cancer by immunohistochemistry. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc***25**, 398-404, doi:10.1038/modpathol.2011.174 (2012).

9 Nahleh, Z. A. *et al.* Male breast cancer in the veterans affairs population: a comparative analysis. *Cancer***109**, 1471-1477, doi:10.1002/cncr.22589 (2007).

10 Anderson, W. F., Jatoi, I., Tse, J. & Rosenberg, P. S. Male breast cancer: a population-based comparison with female breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology***28**, 232-239, doi:10.1200/jco.2009.23.8162 (2010).

11 Gnerlich, J. L. *et al.* Poorer survival outcomes for male breast cancer compared with female breast cancer may be attributable to in-stage migration. *Annals of surgical oncology***18**, 1837-1844, doi:10.1245/s10434-010-1468-3 (2011).

12 Giordano, S. H. *et al.* Adjuvant systemic therapy for male breast carcinoma. *Cancer***104**, 2359-2364, doi:10.1002/cncr.21526 (2005).

13 Vetto, J., Jun, S. Y., Paduch, D., Eppich, H. & Shih, R. Stages at presentation, prognostic factors, and outcome of breast cancer in males. *American journal of surgery***177**, 379-383, doi:10.1016/s0002-9610(99)00067-7 (1999).

14 Berry, D. A. *et al.* Effect of Screening and Ajuvatn Therapy on Mortality form Breast Cancer. (2005).

15 Joshi, M. G. *et al.* Male breast carcinoma: an evaluation of prognostic factors contributing to a poorer outcome. *Cancer***77**, 490-498, doi:10.1002/(sici)1097-0142(19960201)77:3<490::Aid-cncr10>3.0.Co;2-# (1996).

16 Venigalla, S. *et al.* Use and Effectiveness of Adjuvant Endocrine Therapy for Hormone Receptor-Positive Breast Cancer in Men. *JAMA oncology***4**, e181114, doi:10.1001/jamaoncol.2018.1114 (2018).

17 Miao, H. *et al.* Incidence and outcome of male breast cancer: an international population-based study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology***29**, 4381-4386, doi:10.1200/jco.2011.36.8902 (2011).

18 Kiluk, J. V. *et al.* Male breast cancer: management and follow-up recommendations. *The breast journal***17**, 503-509, doi:10.1111/j.1524-4741.2011.01148.x (2011).

19 Fields, E. C., DeWitt, P., Fisher, C. M. & Rabinovitch, R. Management of male breast cancer in the United States: a surveillance, epidemiology and end results analysis. *International journal of radiation oncology, biology, physics***87**, 747-752, doi:10.1016/j.ijrobp.2013.07.016 (2013).

20 McKinley, N., McCain, S. & Kirk, S. Long Term Follow Up of Male Breast Cancer. *The Ulster medical journal***86**, 177-180 (2017).

21 Abrams, M. J., Koffer, P. P., Wazer, D. E. & Hepel, J. T. Postmastectomy Radiation Therapy Is Associated With Improved Survival in Node-Positive Male Breast Cancer: A Population Analysis. *International journal of radiation oncology, biology, physics***98**, 384-391, doi:10.1016/j.ijrobp.2017.02.007 (2017).

22 Sanguinetti, A. *et al.* Male breast cancer in the twenty-first century: What's new? *Annali italiani di chirurgia***85**, 544-550 (2014).

23 Bloom, K. J., Govil, H., Gattuso, P., Reddy, V. & Francescatti, D. Status of HER-2 in male and female breast carcinoma. *American journal of surgery***182**, 389-392, doi:10.1016/s0002-9610(01)00733-4 (2001).

24 Muir, D., Kanthan, R. & Kanthan, S. C. Male versus female breast cancers. A population-based comparative immunohistochemical analysis. *Archives of pathology & laboratory medicine***127**, 36-41, doi:10.1043/0003-9985(2003)127<36:Mvfb>2.0.Co;2 (2003).

25 Haagensen, C. J. D. o. t. B. The surgical treatment of mammary carcinoma. (1971).

26 Hussain, M. A., Ali, S., Tyagi, S. P. & Reza, H. Incidence of cancer breast at Aligarh. *Journal of the Indian Medical Association***92**, 296-297 (1994).

27 Raju, G. C. & Naraynsingh, V. Breast cancer in West Indian women in Trinidad. *Tropical and geographical medicine***41**, 257-260 (1989).

28 Azzena, A. *et al.* Risk factors for breast cancer. Case-control study results. *European journal of gynaecological oncology***15**, 386-392 (1994).

29 Darbre, P. D. Recorded quadrant incidence of female breast cancer in Great Britain suggests a disproportionate increase in the upper outer quadrant of the breast. *Anticancer research***25**, 2543-2550 (2005).

30 Goldhirsch, A., Wood, W. C., Senn, H. J., Glick, J. H. & Gelber, R. D. Fifth International Conference on Adjuvant Therapy of Breast Cancer, St Gallen, March 1995. International Consensus Panel on the Treatment of Primary Breast Cancer. *European journal of cancer (Oxford, England : 1990)***31a**, 1754-1759, doi:10.1016/0959-8049(95)00479-3 (1995).

31 Blum, J. L., Jones, S. E., Fay, J. W., Senzer, N. & Mennel, R. G. Guidelines for systemic therapy of early stage breast cancer. *Breast cancer research and treatment***43**, 259-276, doi:10.1023/a:1005705300012 (1997).

32 Gaffney, D. K., Tsodikov, A. & Wiggins, C. L. Diminished survival in patients with inner versus outer quadrant breast cancers. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology***21**, 467-472, doi:10.1200/jco.2003.12.047 (2003).

33 Lohrisch, C., Jackson, J., Jones, A., Mates, D. & Olivotto, I. A. Relationship between tumor location and relapse in 6,781 women with early invasive breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology***18**, 2828-2835, doi:10.1200/jco.2000.18.15.2828 (2000).

34 Harris, J. R. Natural history of breast cancer. (1996).

35 Urban, J. A. Is there a rationale for an extended radical procedure? *International journal of radiation oncology, biology, physics***2**, 985-988, doi:10.1016/0360-3016(77)90200-0 (1977).

36 Lacour, J. *et al.* Radical mastectomy versus radical mastectomy plus internal mammary dissection. Ten year results of an international cooperative trial in breast cancer. *Cancer***51**, 1941-1943, doi:10.1002/1097-0142(19830515)51:10<1941::aid-cncr2820511032>3.0.co;2-t (1983).

37 Veronesi, U. & Valagussa, P. Inefficacy of internal mammary nodes dissection in breast cancer surgery. *Cancer***47**, 170-175, doi:10.1002/1097-0142(19810101)47:1<170::aid-cncr2820470128>3.0.co;2-c (1981).

38 Morrow, M. & Foster, R. S., Jr. Staging of breast cancer: a new rationale for internal mammary node biopsy. *Archives of surgery (Chicago, Ill. : 1960)***116**, 748-751, doi:10.1001/archsurg.1981.01380180012003 (1981).

39 Zucali, R. *et al.* Early breast cancer: evaluation of the prognostic role of the site of the primary tumor. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology***16**, 1363-1366, doi:10.1200/jco.1998.16.4.1363 (1998).

Tables

Table 1. Disease Characteristics of Male versus Female Breast cancer

	Males (n=1592)	Females (n=220528)	*P*-value
Age (years)			< 0.001
≤40	4 (1.3%)	2320 (5.3%)	
40-49	29(9.5%)	7661 (17.6%)	
50-59	42(13.8%)	10986(25.2%)	
60-69	102(33.4%)	11289(25.9%)	
≥70	128(40.2%)	11396(26.1%)	
Race			< 0.001
White	1264(80.0 %)	172811 (78.9 %)	
Black	238(15.1%)	25119 (11.5%)	
Other	78(4.9%)	21089 (9.6%)	
Laterality			< 0.001
Left	849（53.4%）	111398（50.6%）	
Right	737（46.3 %）	107809（48.9 %）	
Bilateral	5（0.3%）	1205（0.5%）	
Primary Site			< 0.001
Upper-inner	57(3.6%)	26138(11.9%)	
Upper-outer	198(12.4%)	74158(33.6%)	
Lower-inner	29(1.8%)	12057(5.5%)	
Lower-outer	64(4.0%)	15901(7.2%)	
Nipple	85(5.3%)	821 (0.4%)	
Axillary tail	1(0.1%)	1086(0.5%)	
Central portion	605(38.0%)	10105(4.6%)	
Overlapping lesion	242(15.2%)	49397(22.4%)	
Tumor size			< 0.001
T1	645(40.5%)	122805(55.7%)	
T2	660 (40.0 %)	65575(29.7%)	
T3	63(4.0%)	13778(6.2 %)	
T4	139(8.7%)	9511(4.3%)	

Grade			< 0.001
(Well)	169 (10.6%)	45830 (20.8%)	
(Moderately)	774 (48.6 %)	89315 (40.5 %)	
(Poorly)	526(33.0%)	69800(31.7%)	
(Anaplastic)	7(0.4%)	913 (0.4 %)	
Lymph node status			< 0.001
N0	872(54.8%)	143358 (65.0%)	
N1	470(29.5%)	52021(23.6%)	
N2	134(8.4%)	11891(5.4%)	
N3	70(4.4%)	7485 (3.4 %)	
Lymph node metastasis			< 0.001
No	872 54.8%	143358 65.0%	
Yes	674 42.3%	71397 32.4%	
M			< 0.001
M0	1455 (91.4%)	208630(94.6%)	
M1	133 (8.4%)	11739(5.3%)	
Histology			0.001
Ductal	1298 81.5	165449 75.0	
Lobular	11 0.7	18718 8.5	
Others	266 16.7	34098 15.5	
ER			0.001
Positive	1454(91.3%)	174833 (79.3%)	
Negative	49(3.1%)	37531(17.0%)	
PR			0.001
Positive	1346 (84.5%)	151794(68.8 %)	
Negative	145 (9.1%)	59597(17.0%)	
HER2			0.001
Negative	1220(76.6%)	169545(76.9 %)	
Equivocal	52(3.3%)	4616(2.1%)	

Positive	178(11.2%)	31968 (14.5%)	
Surgery			0.001
Yes	1414(88.8)	200248(90.8)	
No	176(11.1)	19796(9.0)	

Table . Multivariate analysis for overall survival of breast cancer stratified by sex

	Men		Women	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age (every10 years)	1.13(1.12-1.41)	0.037	1.18(1.17-1.20)	<0.001
Races				
White	Ref.		Ref.	
Black	1.73(1.07-2.80)	0.025	1.30(1.24-1.36)	<0.001
Others	0.45(0.16-1.28)	0.133	0.82(0.77-0.88)	<0.001
T stages				
T1	Ref.		Ref.	
T2	1.92(1.16-3.26)	0.012	2.23(2.12-2.34)	<0.001
T3	2.27(0.95-5.41)	0.064	3.29(3.09-3.51)	<0.001
T4	2.42(1.15-5.09)	0.020	3.54(3.29-3.80)	<0.001
Grades				
Grade1	Ref.		Ref.	
Grade2	1.45(0.51-4.14)	0.485	1.85(1.70-2.01)	<0.001
Grade3	3.02(1.07-8.51)	0.037	3.13(2.88-3.41)	<0.001
Grade4	17.97(1.73-187.19)	0.016	3.37(2.71-4.19)	<0.001
N stages				
N0	Ref.		Ref.	
N1	1.80(1.11-2.92)	0.018	1.95(1.86-2.04)	<0.001
N2	2.99(1.68-5.32)	0.001	3.27(3.08-3.47)	<0.001
N3	3.25(1.55-6.82)	0.002	3.81(3.58-4.06)	<0.001
M stages				
M0	Ref.		Ref.	
M1	4.67(2.53-8.62)	<0.001	4.24(4.01-4.48)	<0.001
ER				
Negative	Ref.		Ref.	
Positive	0.33(0.13-0.81)	0.016	0.66(0.63-0.70)	<0.001
PR				

Negative	Ref.		Ref.	
Positive	0.68(0.35-1.31)	0.248	0.61(0.58-0.64)	<0.001
HER2				
Negative	Ref.		Ref.	
Positive	0.93(0.54-1.60)	0.795	0.55(0.53-0.58)	<0.001
Surgery				
No	Ref.		Ref.	
Yes	0.35(0.18-0.72)	0.004	0.35(0.33-0.37)	<0.001
Histology				
Ductal	Ref.		Ref.	
Lobular	1.34(0.17-10.81)	0.786	1.09(1.01-1.17)	0.025
Others	0.60(0.27-1.32)	0.202	1.01(0.95-1.06)	0.871
Primary Site				
Internal	Ref.		Ref.	
Central	0.40(0.18-0.89)	0.025	0.94(0.89-0.98)	0.010
Lateral	0.41(0.20-0.84)	0.015	1.03(0.95-1.11)	0.498
Other	0.50(0.22-1.10)	0.084	0.99(0.94-1.04)	0.672

Table . Multivariate analysis for overall survival of breast cancer stratified by sex in CS model

	Men		Women	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age (every10 years)	1.12(1.08-1.41)	0.045	1.18(1.17-1.20)	<0.001
Races				
White	Ref.		Ref.	
Black	1.73(1.07-2.80)	0.025	1.30(1.24-1.36)	<0.001
Others	0.45(0.16-1.28)	0.132	0.82(0.77-0.88)	<0.001
T stages				
T1	Ref.		Ref.	
T2	1.94(1.16-3.26)	0.012	2.23(2.12-2.34)	<0.001
T3	2.27(0.95-5.41)	0.064	3.29(3.09-3.51)	<0.001
T4	2.44(1.160-5.12)	0.019	3.54(3.29-3.80)	<0.001
Grades				
Grade1	Ref.		Ref.	
Grade2	1.45 (0.54-2.68)	0.486	1.85(1.70-2.01)	<0.001
Grade3	3.02(1.07-8.54)	0.037	3.13(2.88-3.41)	<0.001
Grade4	18.68(1.79-194.59)	0.014	3.37(2.71-4.19)	<0.001
N stages				
N0	Ref.		Ref.	
N1	1.80(1.11-2.93)	0.018	2.23(2.12-2.34)	<0.001
N2	3.00(1.68-5.35)	0.001	3.30(3.09-3.52)	<0.001
N3	3.26(1.55-6.85)	0.002	3.54(3.30-3.81)	<0.001
M stages				
M0	Ref.		Ref.	
M1	4.74(2.57-8.75)	<0.001	4.28(4.04-4.52)	<0.001
ER				
Negative	Ref.		Ref.	
Positive	0.33(0.13-0.80)	0.015	0.66(0.62-0.69)	<0.001
PR				

Negative	Ref.		Ref.	
Positive	0.68(0.35-1.31)	0.248	0.61(0.58-0.64)	<0.001
HER2				
Negative	Ref.		Ref.	
Positive	0.93(0.54-1.60)	0.790	0.55(0.52-0.58)	<0.001
Surgery				
No	Ref.		Ref.	
Yes	0.35(0.33-0.37)	0.004	0.35(0.33-0.37)	<0.001
Histology				
Ductal	Ref.		Ref.	
Lobular	1.34(0.17-10.85)	0.024	1.09(1.01-1.17)	0.024
Others	0.60(0.27-1.32)	0.855	1.01(0.95-1.06)	0.855
Primary Site				
Internal	Ref.		Ref.	
Central	0.39(0.18-0.89)	0.025	0.94(0.89-0.99)	0.010
Lateral	0.40(0.19-0.83)	0.014	1.03(0.95-1.11)	0.485
Other	0.49(0.22-1.09)	0.082	0.99(0.94-1.04)	0.688

Table . Multivariate analysis for overall survival of breast cancer stratified by sex in SD model

	Men		Women	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age (every10 years)	1.10(1.01-1.36)	0.041	1.15(1.13-1.17)	<0.001
Races				
White	Ref.		Ref.	
Black	1.65(0.96-2.83)	0.070	1.27(1.21-1.34)	<0.001
Others	0.47(0.16-1.33)	0.152	0.82(0.76-0.88)	<0.001
T stages				
T1	Ref.		Ref.	
T2	1.89(1.11-3.22)	0.019	2.18(2.07-2.30)	<0.001
T3	1.86(0.71-4.90)	0.209	3.21(2.99-3.45)	<0.001
T4	2.10(0.90-4.92)	0.088	3.41(3.14-3.71)	<0.001
Grades				
Grade1	Ref.		Ref.	
Grade2	1.32(0.54-2.68)	0.615	1.85(1.73-2.01)	<0.001
Grade3	2.93(1.03-5.24)	0.065	3.13(2.86-3.34)	<0.001
Grade4	15.82(4.28-58.91)	<0.001	3.41(2.71-4.14)	<0.001
N stages				
N0	Ref.		Ref.	
N1	1.68(1.03-2.76)	0.039	1.96(1.86-2.05)	<0.001
N2	2.77(1.50-5.13)	0.001	3.18(2.98-3.40)	<0.001
N3	3.28(1.48-7.28)	0.004	3.78(3.50-4.08)	<0.001
M stages				
M0	Ref.		Ref.	
M1	4.81(2.467-9.41)	<0.001	4.19(3.93-4.48)	<0.001
ER				
Negative	Ref.		Ref.	
Positive	0.31(0.12-0.81)	0.017	0.68(0.64-0.72)	<0.001
PR				

Negative	Ref.		Ref.	
Positive	0.67(0.35-1.29)	0.229	0.61(0.58-0.65)	<0.001
HER2				
Negative	Ref.		Ref.	
Positive	0.88(0.49-1.59)	0.673	0.57(0.54-0.60)	<0.001
Surgery				
No	Ref.		Ref.	
Yes	0.42(0.19-0.87)	0.020	0.37(0.35-0.40)	<0.001
Histology				
Ductal	Ref.		Ref.	
Lobular	1.65(0.96-2.83)	0.070	1.10(1.02-1.18)	0.012
Others	0.47(0.16-1.33)	0.152	0.99(0.93-1.05)	0.719
Primary Site				
Internal	Ref.		Ref.	
Central	0.40(0.18-0.90)	0.026	0.92(0.87-0.98)	0.005
Lateral	0.40(0.19-0.81)	0.012	1.03(0.95-1.12)	0.503
Other	0.55(0.25-1.19)	0.128	0.98(0.92-1.04)	0.427

Figures

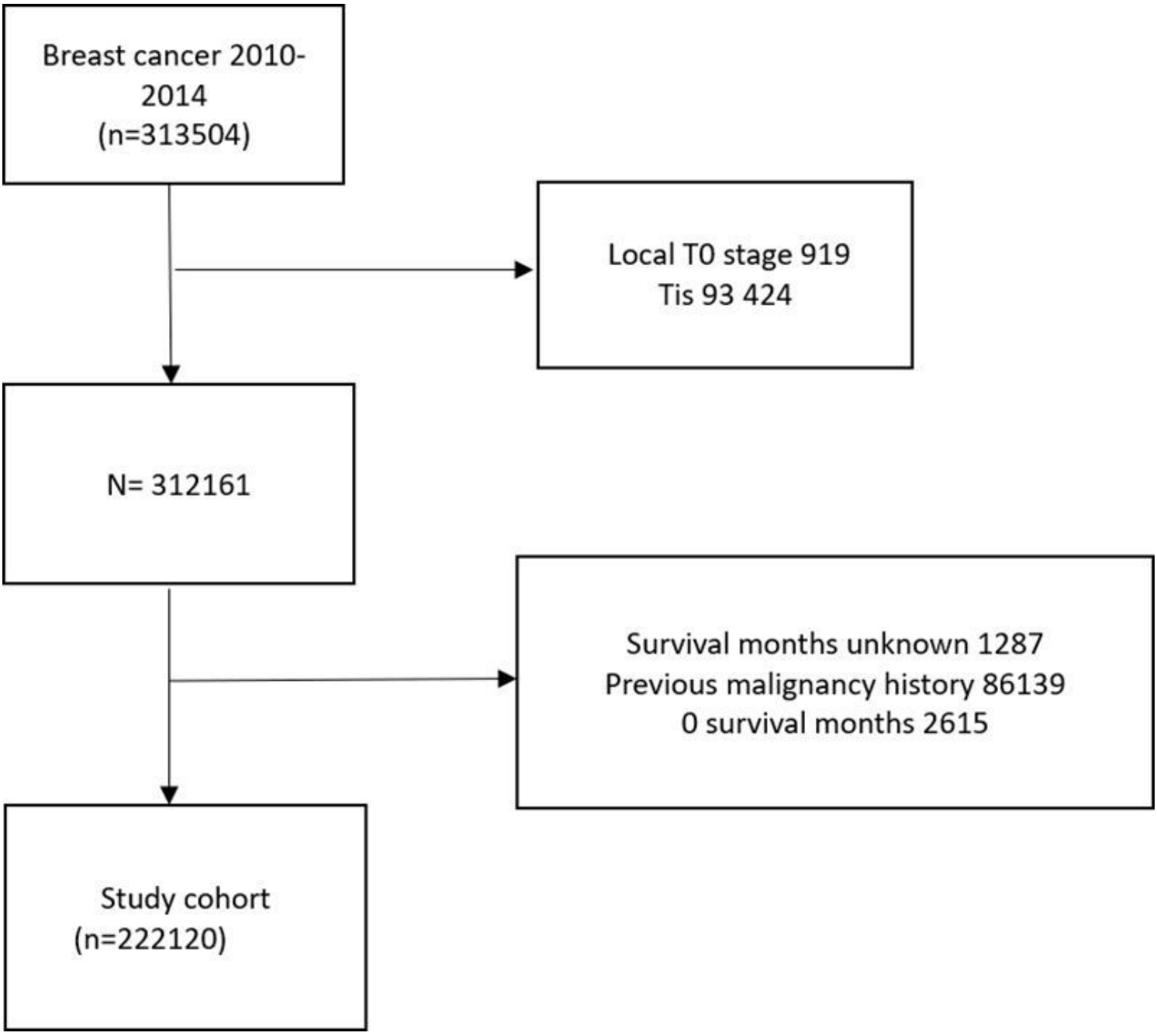

Figure 1

Flow chart of patients' selection for final analysis.

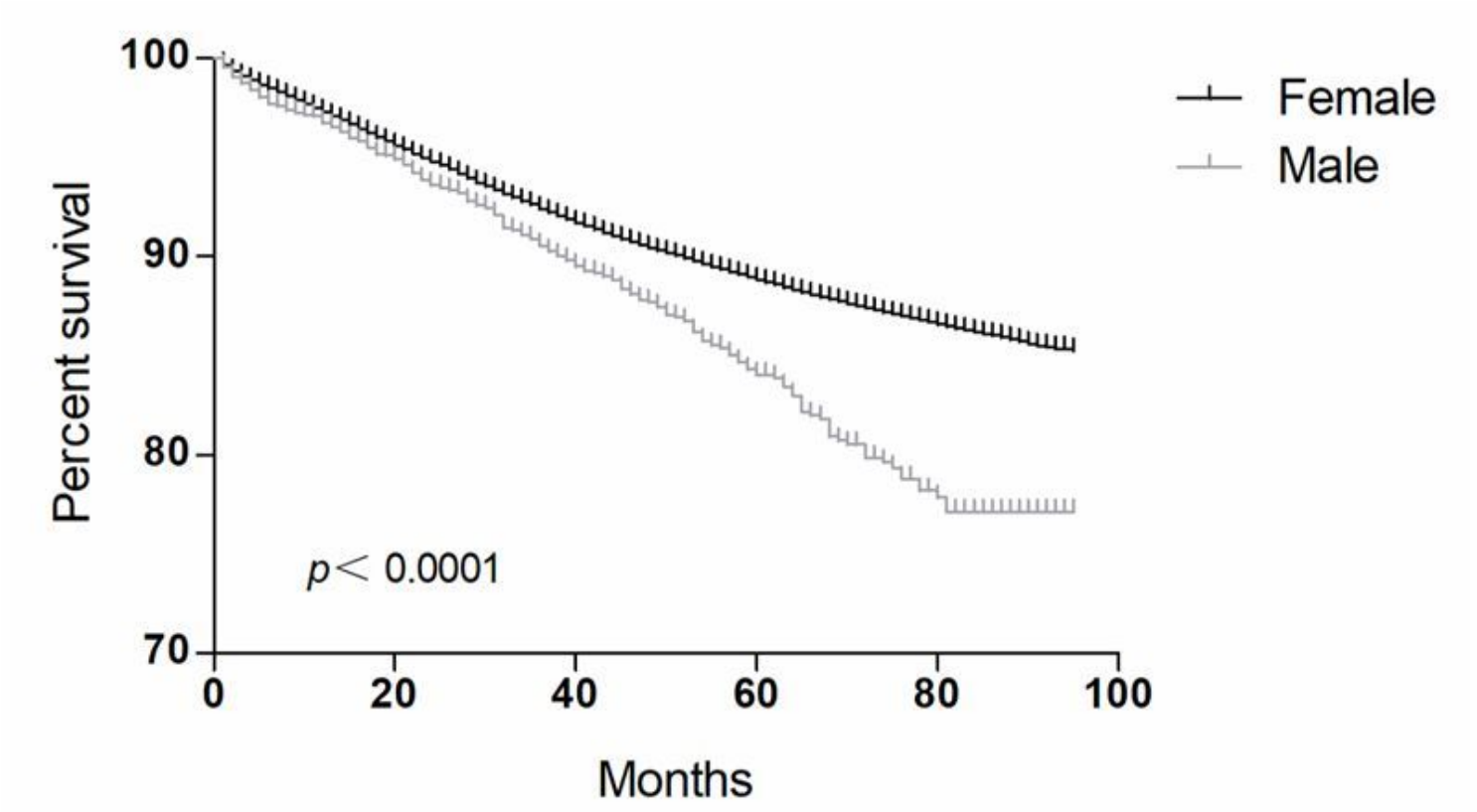

Figure 2

Kaplan-Meier curves showing survival time in the MBC and FBC groups.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx