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Association between Hormone Receptor Status and Prognosis among Male Compared with Female Breast Cancer Patients: 2004-2014 SEER Data

By

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Degree to be awarded: MPH

Epidemiology

_____

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Committee Chair

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By

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MB
Sun Yat-sen University
2016

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2018

ABSTRACT

OBJECTIVES: Male breast cancer (MBC) tends to have more common hormone receptor positivity but worse survival than female breast cancer (FBC). The study aims to explore the effect of hormone receptor on the association between gender and breast cancer prognosis at each tumor stage.
METHODS: 3971 MBC cases and 40,109 FBC cases were obtained from National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database. Multivariate Cox proportional hazard analyses were conducted to explore the hazard ratio of MBC vs. FBC in different hormone receptor strata (ER+, ER-, PR+, PR-) by stage and by age.
RESULTS: The age-adjusted rate of MBC fluctuated between 1.2 per 100,000 and 1.4 per 100,000 from 2004 to 2014. The overall survival of MBC was significantly worse than those of FBC (P<.0001). The 10-year hazard of breast cancer among MBC patients was 1.173 (P < .0001) times the hazard among FBC patients after adjustment for stage. When controlling for all confounders other than hormone status, the hazard ratio of MBC outcome to FBC outcome was 1.115 (P < .0001). MBC had worse survival than FBC in early stage among ER-positive patients (stage I: HR=1.0869; stage II: HR=1.1564) and PR-positive patients (stage I: HR=1.0934; stage II: HR=1.1792).
CONCLUSIONS: There was no significant difference in the 10-year survival of breast cancers which were diagnosed in late stages (III and IV) in each hormone receptor strata. For ER-positive and PR-positive patients, there existed strong differences in the MBC and FBC outcomes in early stage, especially stage II.
KEY WORDS: SEER, Male breast cancer, prognosis, hormone receptor

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Chapter I

LITERATURE REVIEW

Male breast cancer is about 100 times less common than female breast cancer. Due to its rarity, in early years, clinicians tended to treat male breast cancer in the same way as they treat female breast cancer. Researchers didn't realize that men had different breast cancer clinicopathological characteristics from women. In addition, most of the research that concerned male breast cancer was from observational studies, especially retrospective cohort studies. Few randomized trials were conducted regarding the epidemiology, treatment and prognosis of male breast cancer. Experimental studies always failed to recruit enough male breast cancer patients to guarantee the reliability of the studies (1).

A study based on the National Cancer Institute's Surveillance, Epidemiology, and End Results database from 1973–1998 examined the differences between male and female breast cancer (2). The median age at diagnosis for male breast cancer was 67 years while the median age at diagnosis for females was slightly younger at 62 years. There were significant differences in tumor stage, tumor size, and lymph node status between males and females with breast carcinoma. Males appeared to have higher stage at diagnosis, larger tumor size and greater lymph node positivity. Among individuals with known PR status, 81.2% of males compared to 66.7% of females had PR-positive disease. The proportions of ER-positive disease among individuals with known ER status were 90.6% in men and 76.0% in women.

An observational study which recruited cases from the End Results Evaluation Program of National Cancer Institute and three statewide tumor registry systems suggested that females had a higher percentage of patients surviving five-years after breast cancer diagnosis than males (3). While these results were partially explained by the lack of awareness of this disease in men thus resulting in a later stage at the time of diagnosis, the investigators found that the survival

advantage among women persisted at each stage of disease.

These gender-specific differences in breast cancer survival could also be related to the disparities of genetic and hormonal environment and the anatomic constitution in men, including BRCA2 gene, the sex chromosome type and other unknown biological differences (4).

Since the prognosis of breast cancer was found to be poorer in males than in females, a series of 257 cases of male breast cancer in Denmark was examined to analyze the potential factors that might influence the prognosis of male breast cancer (5). In this study, the author indicated six potential factors, including age at diagnosis, duration of symptoms, TNM stage at diagnosis, tumor size, histological grade of malignancy and treatment. Individuals who were diagnosed before the age of 65 had higher adjusted five-year all-cause survival than individuals who were diagnosed after the age of 65 (47.5% vs. 43.9%). There was no significant difference in the corrected ten-year survival rate between the two age groups (28.8% vs. 29.3%), however. The five-year survival rate of individuals with a duration of symptoms of one year or more was better than those of individuals with less duration of symptoms. The advanced clinical TNM stage at diagnosis of disease carried a significantly worse prognosis for both five- and ten-year survival. The five-year survival rate decreased significantly with increasing size of tumor. The survival rate carried a significant decrease with the advance of tumor grade.

With the incorporation of endocrine therapy in breast cancer treatment, more and more studies suggested that there existed a different frequency of hormone receptor status among male breast cancer patients relative to female patients (6-9). Male and female breast cancer differ in the expression of steroid hormone receptors. Men are more likely to have estrogen receptor positivity and progesterone receptor positivity (10-12).

An international meta-analysis concerning the association between biomarkers and the outcome of male breast cancer analyzed the effect of several biomarkers including ER, PR and HER2. The cohort study gathered data from 15 published studies and assembled 1984 male breast cancer cases. The univariate analysis of biomarkers showed that ER positivity and PR positivity had no

significant effect on the overall survival of male breast cancer (ER: HR = 1.00, 95%CL = 0.48, 2.12; P =0.99. PR: HR = 1.01, 95%CL = 0.57, 1.81; P =0.96). For disease free survival, the univariate analysis of ER presented a harmful but insignificant effect while those of PR presented a protective but insignificant effect (ER: HR = 1.12, 95%CL = 0.15, 8.22; P =0.91. PR: HR = 0.97, 95%CL = 0.43, 2.19; P =0.94) (13). However, these results had not been compared with those among females. A separate study comparing differences between genders concluded that male patients with HR+/HER2- breast cancer appeared to have worse overall survival in early stage (I and II) disease than female breast cancer patients but better overall survival in late stage (III and IV) disease. The hazard ratio (male vs. female) of overall survival in breast cancer with HR+/HER2+ increased with the advancing of tumor stage but decreased in stage IV (14).

Previous breast cancer studies tended to take menopausal status into consideration. It is presumed that estrogen levels have a different effect on hormone related cancer among premenopausal women and postmenopausal women (15). However, discussion regarding menopausal status is rare in studies regarding disparities between men and women.

The primary limitations of past studies are small sample sizes, limited diagnosis years and inadequate comparisons between different genders. To address this gap in knowledge, this retrospective cohort study used patient information from the population-based Surveillance, Epidemiology, and End Results (SEER) registry over the most recent 10-year period available. The study aims to explore whether hormone receptors make a difference in the association between gender and breast cancer prognosis at each tumor stage as well as the role of hormone status on the relationship between gender and breast cancer outcomes.

Chapter II

ABSTRACT

Association between Hormone Receptor Status and Prognosis among Male Compared with Female Breast Cancer Patients: 2004-2014 SEER Data

By Xiaowen Hu

OBJECTIVES: Male breast cancer (MBC) tends to have more common hormone receptor positivity but worse survival than female breast cancer (FBC). The study aims to explore the effect of hormone receptor on the association between gender and breast cancer prognosis at each tumor stage.
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KEY WORDS: SEER, Male breast cancer, prognosis, hormone receptor

INTRODUCTION

Male breast cancer is a rare disease with approximately 2,000 new cases diagnosed in the U.S. each year. American Cancer Society estimated that about 2,550 new cases of invasive male breast cancer will be diagnosed in 2018 in the United State (1). Less than 1% of all breast cancer develops in males. In the period of 1988-2002, the incidence rate of male breast cancer in the United States was 0.72 per 100,000(0.69, 0.76), with the female-to-male incidence rate ratio of 125.8 (119.8, 132.3) (16). The 2004-2014 National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database recorded 809,397 new cases of breast cancer (including

carcinoma in situ and malignant tumor) diagnosed during this period in the United States. Only 5,544 of these cases were among men. Potential risk factors for breast cancer include gender, age, race/ethnicity, genetic mutation status, hormone levels, smoking and alcohol (17). Previous research indicates that male breast cancer has a worse prognosis than female breast cancer (3, 5, 18-19). Compared with female breast cancer, male breast cancer patients had a higher median age at diagnosis and were more likely to have lymph node invasion, advanced stage at diagnosis, and positive hormone receptor status (estrogen and progesterone) (4). Previous research also suggests that male breast cancer has more advanced stage-related tumor characteristics (tumor size >2 cm and positive axillary lymph nodes) than female breast cancer (20). Although the survival disparity is thought to be due to the tendency toward later stage at diagnosis of male breast cancer, the disease-free survival rates and overall survival rates of breast cancer also differed by gender when matching on stage at diagnosis (14, 21).

Despite these studies, limited research has focused on the comparison of prognosis between male breast and female breast cancer patients and the role of hormone receptor status in explaining observed differences in outcomes. Around 90% of male breast cancers are estrogen receptor positive (ER+) and 81% progesterone receptor positive (PR+) (22). The percent of hormone receptor positive tumors is lower among women.

The major objective of this study is to determine whether the association between hormone receptor status and prognosis among male breast cancer is significantly different from that of female breast cancer when controlling for stage at diagnosis in the United States. What role does hormone receptor status play in explaining observed survival differences after controlling for tumor stage and other confounders?

METHODS

Data Collection

Patient information was obtained from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database derived from 18 registries. The study reviewed all registered cases of invasive and in situ breast carcinoma diagnosed from 2004 to 2014 in the SEER coverage areas and identified 5,544 new cases of male breast cancer as well as 803,853 new cases of female breast cancer. We excluded the cases which were found at autopsy or the only information was from a death certificate. Individuals with missing values on survival months, AJCC stage, demographic information including race/ethnicity, marital status, sequence number and unclear hormone receptor status and were excluded from the study. For duplicated records with the same patient number, the one with larger sequence number was removed. Figure 1 provides a flowchart showing the number of male cases exclusions in the study cohort. 5514 registered male cases provided information of survival months, 733 of them were excluded due to unclear hormone status, 588 were excluded for ineligible stage, 199 were excluded for missing data on demographic information and 53 duplicated patients were removed. A random sample of 40,109 cases were selected from the eligible 529,181 female breast cancer cases by the original age*race/ethnicity*stage strata within the female population.

Age at diagnosis was recorded as continuous variables, and was defined as binary variables (<60: younger than 60 years, ≥60: 60 or older than 60 years) when conducting univariate Cox proportional hazard analysis. Five categories of race/ethnicity were non-hispanic White, non-hispanic black, non-hispanic Asian and Pacific islander, non-hispanic American Indian/Alaska native, and Hispanic. Marital status at diagnosis, surgical treatment and sequence number were binary variables that respectively indicated whether the patient was married, had surgery, and had other cancers in their lifetime. AJCC tumor stage was categorized as stage I, II, III and IV.

Statistical Analysis

Of the 3,971 male and 40,109 female breast cancer that were eventually included in the current retrospective cohort study, the median follow-up was 40 months for the men (range, 0-131 months) and 48 months for the women (range, 0-131 months). Survival analyses were based on all causes

of death. Kaplan-Meier curve and log-rank tests for the overall survival of male and female breast cancer was constructed. The overall survival (OS) was defined as survival during the time from initial diagnosis to death, lost to follow-up or study endpoint. Hazard ratios (HRs) were determined by Cox regression with 95% confidence limits (95% CLs). Data were analyzed using univariate Cox proportional hazard model for gender and hormone receptor status in all cases. Multivariate Cox regression analyses included the variables ER status, PR status, gender, age, race/ethnicity, tumor stage at diagnosis, marital status, surgical treatment, tumor sequence number as well as the interaction between hormone receptor and gender. Interaction assessment of hormone receptor on gender were evaluated by wald test. The hazard ratio (male vs. female) of breast cancer was assessed in subgroups of tumor stage at diagnosis and subgroups of age by hormone receptor strata to compare the role of hormone receptors on the relationship between gender and breast cancer outcomes in different tumor stages and age groups.

All significance levels reported (P values) are two-sided, and P-values below 0.05 were regarded as statistically significant. All analyses were carried out with SAS version 9.4 software.

RESULTS

For male breast cancer cases registered from 2004 to 2014, the incidence of breast cancer was generally increasing. Incidence ranged from 406 cases in 2004 to 592 cases in 2014 (Figure 2). The age-adjusted rate was generally stable with the fluctuation between 1.2 per 100,000 and 1.4 per 100,000 (Figure 3). In 2007, incidence rose to 508 cases while the age-adjusted rate reached the peak of 1.4 per 100,000.

For the sample of cases in this study, the median follow-up for 3971 male breast cancer cases was 40 months, ranging from 0 to 131 months. 40,109 female breast cancer cases had a significantly higher median follow-up of 48 months ($P < 0.05$), also ranging from 0 to 131 months. The distribution of predictors and potential confounding factors that were considered in the multivariate

Cox regression analyses are summarized for male cases and female cases in Table 1. Each characteristic demonstrated statistically significant differences between breast cancer cases in male and female patients with P<.0001 in a 2-sample t test for age at diagnosis and χ^2 test for other characteristics, except for treatment. Male breast cancer patients had a higher proportion diagnosed before the age of 60 (73.9% vs. 53.5%; P < 0.05), higher ER positivity (96.1% vs. 80.8%; P < 0.05) and higher PR positivity (87.7% vs. 69.6%; P < 0.05). In addition, men were more likely to be diagnosed with breast cancer at later stages. The proportions diagnosed at stage I were 31.7% for male and 48.4% for female while the proportions of being diagnosed at stage IV were 7.4% for male and 4.9% for female.

The Kaplan-Meier curve indicated that female breast cancer cases had a significant higher survival status than male breast cancer cases at every point of follow-up, with a P < .0001 log-rank test (Figure 4).

The 10-year univariate Cox proportional hazard analyses showed slight but significant hazard ratio of males to females (Table 2). The hazard of breast cancer among men was 1.238 (95% CL = 1.189, 1.288; P < .0001) times the hazard among women in 5 years since diagnosis. The breast cancer hazard ratio of male to female in 10 years since diagnosis was similar to those in 5 years since diagnosis (HR = 1.221, 95%CL = 1.181, 1.262; P < .0001). Patients with ER /PR positivity at diagnosis had significantly better survival than patients with ER/PR negativity in 5 years since diagnosis (ER: HR = 0.951, 95%CL = 0.922, 0.981; P = 0.0016; PR: HR = 0.973, 95%CL = 0.948, 0.999; P = 0.0458). However, ER or PR positivity didn't show significantly protective effect on the hazard of breast cancer in 10 years since diagnosis (ER: HR = 0.995, 95%CL = 0.971, 1.020; P = 0.7052; PR: HR = 1.004, 95%CL = 0.983, 1.026; P = 0.6993).

The 10-year hazard ratio of males versus female breast cancer for different stages at diagnosis are presented in Table 3. For multivariate Cox regression analyses that stratified by ER, adjusted confounders were PR status, age, tumor stage, race/ethnicity, marital status, surgical treatment, tumor sequence number and the interaction term was ER*gender. Hazard ratios (MBC vs. FBC)

with ER positivity and ER negativity were respectively performed in ER-Positive strata and ER-Negative strata to see the mediated effect of ER status. Likewise, adjusted confounders for 10-year survival analyses that stratified by PR were ER status, age, tumor stage, race/ethnicity, marital status, surgical treatment, tumor sequence number and the interaction term was PR*gender. Results were presented by hormone status to see whether the association of hormone receptor status and breast cancer outcomes differ in gender when controlling for tumor stage. Comparison of the all cases combined group that only adjusted for stage and the hormone status stratified groups that adjusted for all covariates except for hormone status aimed to figure out the additional effect on the hazard ratio of adjusting for these other covariates. Hazard ratios (MBC vs. FBC) mediated by PR status were respectively demonstrated in PR-Positive strata and PR-Negative strata. After controlling for tumor stage, the 10-year hazard of breast cancer among MBC patients was 1.173 (95% CL = 1.135, 1.213; P < .0001) times the hazard among FBC patients. When controlling for all confounders other than hormone status, the hazard ratio was 1.115 (95% CL = 1.075, 1.158; P < .0001). For ER status, the adjusted hazard ratio of MBC to FBC was 1.1174 (95% CL = 1.0740, 1.1626; P < .0001) for ER-positive patients and 1.0781 (95% CL = 0.8724, 1.3322; P < 0.4863) for ER-negative patents, with no significant evidence of interaction (P = 0.7441). As to PR status, adjusted hazard among MBC patients was 1.1341 (95% CL = 1.0888, 1.1812; P < .0001) times those among FBC patients in cases with PR-positivity. The association of breast cancer survival and gender demonstrated a lower but non-significant hazard ratio of MBC to FBC among PR-negative patients (HR = 1.0363, 95%CL = 0.9268, 1.1587; P = 0.5318). Interaction of PR status and gender was significant after controlling for stage at diagnosis combined (P = 0.0136).

In table 3, MBC demonstrated better but nonsignificant 10-year survival of breast cancer in ER-negative subgroup that diagnosed at stage I (HR = 0.8468, 95%CL = 0.5479, 1.3088; P = 0.4541) and PR-negative subgroup that diagnosed at stage II (HR = 0.9590, 95%CL = 0.8069, 1.1397; P = 0.6345). Statistically significant evidence of interaction between PR status and gender was only showed in patients who diagnosed at stage I (P = 0.0266). None of the stage subgroups indicated

significant interaction between ER status and gender.

Table 4 showed the hazard ratio of MBC to FBC by age subgroups. MBC inferred better but nonsignificant 10-year survival of breast cancer in ER-negative subgroup that diagnosed under the age of 60 (HR = 0.8903, 95%CL = 0.6031, 1.3350; P = 0.5930) and PR-negative subgroup that diagnosed under the age of 60 (HR = 0.8488, 95%CL = 0.6945, 1.0375; P = 0.1095). Significant interaction between PR and gender was found in patients who diagnosed under the age of 60 (P = 0.0074). However, there was no evidence of interaction between ER status and gender. The highest hazard ratio in stage subgroups was showed among ER-negative patients who diagnosed at stage IV (HR = 1.5216, 95%CL = 0.8158, 2.8382; P = 0.1869). Whereas, the highest hazard ratio in age subgroups was showed among PR-negative patients who diagnosed at or over the age of 60 (HR = 1.1450, 95%CL = 1.0007, 1.3102; P = 0.0489).

DISCUSSION

In the retrospective cohort study based on SEER database, breast cancer cases were derived from 18 registries including Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, the Alaska Native Tumor Registry, Greater California, Greater Georgia, Kentucky, Louisiana, and New Jersey. Due to the rarity of male breast cancer, previous studies that collected data from hospitals or other health centers tended to have small male breast cancer sample sizes. One of the main strengths in this study is the large sample of male breast cancer patients included. However, of the 5544 diagnosed male breast cancer cases, 1573 cases were excluded because of missing information. The major missing information included unknown ER/PR status, borderline ER/PR status and unknown demographic information. Selection bias also could be induced due to the smaller sample size selected from the eligible 529,181 female breast cancer cases by the original age*race/ethnicity*stage strata.

Previous published studies suggested that poorer survival of male breast cancer might result from

older age and advanced tumor grade at diagnosis as well as higher incidence of lymph node metastases (19, 22-24). The Kaplan-Meier curve indicated a significant disparity of prognosis among male and female breast cancer. Male breast cancer had poorer survival than female breast cancer over the 10 years study period.

In the multivariate Cox proportional hazard analysis, there was no significant difference in the 10-year survival of breast cancers which were diagnosed in late stages (III and IV) in each hormone receptor strata. This inferred that 10-year survival showed no difference in male and female breast cancer diagnosed in stage III and stage IV regardless of the hormone status. For ER-positive and PR-positive patients, there existed strong differences in the outcomes of male vs. female in early stage disease, especially in stage II. The results were consistent with previous study that suggested HR+ MBC patients have worse survival than HR+ FBC patients in early stage (14).

When comparing the all cases combined group that only adjusted for stage and the hormone status stratified groups that adjusted for all covariates except for hormone status, receptor-positive groups had almost identical HR within each stage groups to the combined group that controlled for every covariate other than receptor status. This was not the case with the receptor negative groups. Results in the combined models were largely made up of the receptor positive patients as almost all male patients were receptor positive. Comparison of all cases combined group that adjusted for everything except for hormone receptor and ER-positive strata showed similar hazard ratio in each stage. Controlling for ER status didn't show great effect on the difference of breast cancer outcomes. However, PR-positive strata had stronger differences in cancer outcomes than all cases combined group that adjusted for everything except for hormone receptor in late stages (III and IV).

In the multivariate Cox proportional hazard analysis by age, no difference of MBC survival and FBC survival was showed in ER-negative patients and PR-negative patients. On the contrary, ER-positive MBC patients and PR-positive MBC patients had worse outcomes than FBC patients in the same strata. For ER-positive patients, differences in MBC and FBC survival were stronger among patients who diagnosed over the age of 60 than those who diagnosed before the age of 60. For PR-

positive patients, there was no obvious survival differences in the under 60 group and the over 60 group.

Interaction terms of PR status and gender demonstrated significant effect among patients diagnosed at stage I and patients diagnosed under the age of 60. Diagnosed at early age and diagnosed at early stage were considered as the population with less hazard of developing breast cancer and better survival (25). It inferred that the association between gender and breast cancer prognosis among PR-Positive patients significantly different from those of PR-Negative patients when controlling for stage at diagnosis in less vulnerable population. However, ER status didn't show significant mediated effect on the association between gender and prognosis in the study.

Male breast cancer patients are still treated as female breast cancer despite of the difference in hormone receptor distribution (26). Although male breast cancer patients have higher positivity in ER and PR status, the proportion of surgical treatment and hormone therapy are similar in both gender. Biomarker status including ER, PR and HER2 was indicator of cancer screening and treatment. Previous research stated that 37% of the reduction in overall female breast cancer mortality rate was associated with screening while 27% was associated with hormone therapy in the United States (27). The disparity of prognosis in gender could help set different thresholds of cancer screening and explore different treatment for each gender.

REFERENCES

1. Society AC. About Breast Cancer in Men: Get an overview of breast cancer in men and the latest key statistics in the US. Secondary About Breast Cancer in Men: Get an overview of breast cancer in men and the latest key statistics in the US 2016. https://www.cancer.org/cancer/breast-cancer-in-men/about.html.
2. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN. Breast carcinoma in men: a population-based study. Cancer 2004;**101**(1):51-7 doi: 10.1002/cncr.20312[published Online First: Epub Date]|.
3. Moss NH. Cancer Of The Male Breast. Annals of The New York Academy of Sciences 1964;**114**:937-50
4. Rudlowski C. Male Breast Cancer. Breast Care (Basel) 2008;**3**(3):183-89 doi: 10.1159/000136825[published Online First: Epub Date]|.
5. SCHEIKE O. Male Breast Cancer- Factor influencing prognosis. British Journal of Cancer 1974;**30**:261–71 doi: 10.1038/bjc.1974.190[published Online First: Epub Date]|.
6. Nomura Y KJYJ, Takenaka K. Detection of estrogen receptor and response to endocrine therapy in male breast cancer patients. Grinti 1977;**68**:333-36
7. Rosen PP M-BC, Nisselbaum JS, Schwartz MK, Urban JA. Estrogen receptor protein in lesions of the male breast.A preliminary report. Cnricc.r 1976;**27**:1866-68
8. Gupta N, Cohen, J. L., Rosenbaum, C. and Raam, S. Estrogen receptors in male breast cancer. Cancer 1980;**46**:1781-84 doi: 10.1002/1097-0142(19801015)46:8<1781::AID-CNCR2820460814>3.0.CO;2-F[published Online First: Epub Date]|.
9. Leclerq G VA, Deboel MC, et al. Oestrogen receptors in male breast cancer. Biomedicine 1976;**25**:327-30
10. Malani AK. Male breast cancer: A different disease than female breast cancer? Southern Medical Journal 2007;**100**(2)
11. Friedman MA HPJ, Dandolos EM, Lagios MD,Johnston WH, Siiteri PK. Estrogen receptors in male breast cancer: clinical and pathologic correlations. Cancer 1981;**47**:134-37
12. Stalsberg H TD, Rosenblatt KA, et al. Histologic types and hormone receptors in breast cancer in men: a population-based study in 282 United States men. Cancer Causes Control 1993;**4**:143-51
13. Humphries MP, Sundara Rajan S, Honarpisheh H, et al. Characterisation of male breast cancer: a descriptive biomarker study from a large patient series. Sci Rep 2017;**7**:45293 doi:

10.1038/srep45293[published Online First: Epub Date]|.

14. Li X, Yang J, Krishnamurti U, et al. Hormone Receptor-Positive Breast Cancer Has a Worse Prognosis in Male Than in Female Patients. Clin Breast Cancer 2017;**17**(5):356-66 doi: 10.1016/j.clbc.2017.03.005[published Online First: Epub Date]|.
15. Robert Hoover LAG, Philip Cole, Brian MacMahon. Menopausal Estrogens and Breast Cancer. The New England Journal of Medicine 1976;**295**(8):401-05
16. Ly D, Forman D, Ferlay J, Brinton LA, Cook MB. An international comparison of male and female breast cancer incidence rates. Int J Cancer 2013;**132**(8):1918-26 doi: 10.1002/ijc.27841[published Online First: Epub Date]|.
17. Sun. H-F, Zhao. Y, Gao. S-P, et al. Clinicopathological characteristics and survival outcomes of male breast cancer according to race. Oncotarget 2017
18. John N. Classen MACWM, MD; and Shaw Wilgis, MD, Baltimore. Cancer in the Male Breast. Arch Surg. 1970;**100**(1):66-67
19. B. Salvadori RS, A. Manzari, S. Andreola, R.A. Conti, F. Cusumano, M. Grassi. Prognosis of breast cancer in males: an analysis of 170 cases. European Journal of Cancer 1994;**30A**:930-35
20. Maurer C, Martel S, de Azambuja E. Male breast cancer: finding the way in this uncommon path. ESMO Open 2017;**2**(1):e000169 doi: 10.1136/esmoopen-2017-000169[published Online First: Epub Date]|.
21. Chen X, Liu X, Zhang L, Li S, Shi Y, Tong Z. Poorer survival of male breast cancer compared with female breast cancer patients may be due to biological differences. Jpn J Clin Oncol 2013;**43**(10):954-63 doi: 10.1093/jjco/hyt116[published Online First: Epub Date]|.
22. Naoko Tajima HT, Akira Oshima. A Descriptive Epidemiology of Male Breast Cancer in Osaka, Japan. Journal of Epidemiology 2000;**11**:1-7
23. Miao H, Verkooijen HM, Chia KS, et al. Incidence and outcome of male breast cancer: an international population-based study. J Clin Oncol 2011;**29**(33):4381-6 doi: 10.1200/JCO.2011.36.8902[published Online First: Epub Date]|.
24. William L. Donegan PNR, Peter J. Lang, Matthew T. Gall. Carcinoma of the breast in males: a multiinstitutional survey. American Cancer Society 1998;**83**(3):498-509
25. Huo D, Perou CM, Olopade OI. Reported Biologic Differences in Breast Cancer by Race Due to

Disparities in Screening-Reply. JAMA Oncol 2018 doi: 10.1001/jamaoncol.2017.5909[published Online First: Epub Date]|.

26. Wan BA, Ganesh V, Zhang L, et al. Treatment Outcomes in Male Breast Cancer: A Retrospective Analysis of 161 Patients. Clin Oncol (R Coll Radiol) 2018 doi: 10.1016/j.clon.2018.02.026[published Online First: Epub Date]|.

27. Plevritis SK, Munoz D, Kurian AW, et al. Association of Screening and Treatment With Breast Cancer Mortality by Molecular Subtype in US Women, 2000-2012. JAMA 2018;**319**(2):154-64 doi: 10.1001/jama.2017.19130[published Online First: Epub Date]|.

TABLES

Table 1. Distribution of Factors for Male Cases and Female Cases

Characteristic	No. of Male (%)	No. of Female (%)	P-value
	TOTAL=3,971	TOTAL=40,109	
Age at Diagnosis			<0.0001
<60	2,936 (73.9)	21,458 (53.5)	
≥60	1,035 (26.0)	18,651 (46.5)	
Race/Ethnicity			<0.0001
Non-Hispanic White	2,996 (75.4)	28,557 (71.2)	
Non-Hispanic Black	544 (13.7)	4,252 (10.6)	
Non-Hispanic American Indian/Alaska Native	9 (0.2)	201 (0.5)	
Non-Hispanic Asian or Pacific Islander	181 (4.6)	3,128 (7.8)	
Hispanic (All Races)	241 (6.1)	3,971 (9.9)	
Stage			<0.0001
I	1,258 (31.7)	19,393 (48.4)	
II	1,719 (43.3)	13,828 (34.5)	
III	701 (17.7)	4,917 (12.3)	
IV	293 (7.4)	1,971 (4.9)	
ER Status			<0.0001
Positive	3,815 (96.1)	32,408 (80.8)	
Negative	156 (3.9)	7,701 (19.2)	
PR Status			<0.0001
Positive	3,483 (87.7)	27,916 (69.6)	
Negative	488 (12.3)	12,193 (30.4)	
Single Cancer in Lifetime			<0.0001
Yes	2,717 (68.4)	30,563 (76.2)	
No	1,254 (31.6)	9,546 (23.8)	
Experienced Surgical Treatment			0.1497
No	265 (6.7)	2,447 (6.1)	
Yes	3,706 (93.3)	37,662 (93.9)	

Each characteristic demonstrated statistically significant differences between breast cancer cases in male and female patients with P<.0001 in a 2-sample t test for age at diagnosis and χ^2 test for other characteristics except for treatment.

Table 2. Univariate Cox Proportional Hazard Analysis

	5-year Hazard Ratio	P	10-year Hazard Ratio	P
Gender (male vs. female)	1.238 (1.189, 1.288)	<.0001	1.221 (1.181, 1.262)	<.0001
ER (ER+ vs. ER-)	0.951 (0.922, 0.981)	0.0016	0.995 (0.971, 1.020)	0.7052
PR (PR+ vs. PR-)	0.973 (0.948, 0.999)	0.0457	1.004 (0.983, 1.026)	0.6993

Table 3. All Cases Combined and ER/PR Status Subgroups Multivariate Cox Proportional Hazard Analysis for 10-year Survival by Stage

	Hazard Ratio MBC vs. FBC	95% CI	P-value
All Cases Combined[b]	1.173	1.135, 1.213	<.0001 [a]
Stage I	1.156	1.091, 1.226	<.0001 [a]
Stage II	1.225	1.264, 1.289	<.0001 [a]
Stage III	1.133	1.046, 1.228	0.0023 [a]
Stage IV	1.061	0.938, 1.200	0.3466
All Cases Combined[c]	1.115	1.075, 1.158	<.0001 [a]
Stage I	1.097	1.031, 1.167	0.0035 [a]
Stage II	1.154	1.091, 1.220	<.0001 [a]
Stage III	1.061	0.964, 1.169	0.2240
Stage IV	1.076	0.894, 1.294	0.4376
ER-Positive[d]	1.1174	1.0740, 1.1626	<.0001 [a]
Stage I	1.0869	1.0191, 1.1591	0.0112 [a]
Stage II	1.1564	1.0902, 1.2267	<.0001 [a]
Stage III	1.1031	0.9913, 1.2276	0.0718
Stage IV	1.0598	0.8442, 1.3305	0.6166
ER-Negative[d]	1.0781	0.8724, 1.3322	0.4863
Stage I	0.8468	0.5479, 1.3088	0.4541
Stage II	1.0969	0.7961, 1.5112	0.5717
Stage III	1.0284	0.6105, 1.7324	0.6166
Stage IV	1.5216	0.8158, 2.8382	0.1869
PR-Positive[e]	1.1341	1.0888, 1.1812	<.0001 [a]
Stage I	1.0934	1.0233, 1.1684	0.0083 [a]
Stage II	1.1792	1.1097, 1.2531	<.0001 [a]
Stage III	1.1268	1.0103, 1.2568	0.0320 [a]
Stage IV	1.1714	0.9292, 1.4767	0.1807
PR-Negative[e]	1.0363	0.9268, 1.1587	0.5318
Stage I	1.0444	0.8558, 1.2746	0.6688
Stage II	0.9590	0.8069, 1.1397	0.6345
Stage III	1.0058	0.7680, 1.3173	0.9662
Stage IV	1.3122	0.8708, 1.9774	0.1940

10-year survival was based on all cause death.

[a] Statistically significant.

[b] Multivariate Cox Proportional Hazard Analyses were adjusted for stage.

[c] Multivariate Cox Proportional Hazard Analyses were adjusted for age, stage, race/ethnicity, marital status, treatment and sequence number

[d] Multivariate Cox Proportional Hazard Analyses were adjusted for PR status, age, stage, race/ethnicity, marital status, treatment and sequence number, interaction of ER status and gender.

[e] Multivariate Cox Proportional Hazard Analyses were adjusted for ER status, age, stage, race/ethnicity, marital status, treatment and sequence number, interaction of PR status and gender.

Table 4. All Cases Combined and ER/PR Status Subgroups Multivariate Cox Proportional Hazard Analysis for 10-year Survival by Age

	Hazard Ratio MBC vs. FBC	95% CI	P-value
All Cases Combined[b]	1.125	1.181, 1.170	<.0001 [a]
<60	1.115	1.033, 1.203	0.0050 [a]
≥60	1.129	1.077, 1.182	<.0001 [a]
ER-Positive[c]	1.1174	1.0740, 1.1626	<.0001 [a]
<60	1.1007	1.0201, 1.1877	0.0135 [a]
≥60	1.1247	1.0737, 1.1782	<.0001 [a]
ER-Negative[c]	1.0781	0.8724, 1.3322	0.4863
<60	0.8903	0.6031, 1.3350	0.5930
≥60	1.1413	0.8876, 1.4675	0.3027
PR-Positive[d]	1.1341	1.0888, 1.1812	<.0001 [a]
<60	1.1396	1.0532, 1.2330	0.0012 [a]
≥60	1.1323	1.0797, 1.1786	<.0001 [a]
PR-Negative[d]	1.0363	0.9268, 1.1587	0.5318
<60	0.8488	0.6945, 1.0375	0.1095
≥60	1.1450	1.0007, 1.3102	0.0489 [a]

10-year survival was based on all cause death.

[a] Statistically significant.

[b] Multivariate Cox Proportional Hazard Analyses were adjusted for ER status, PR status, age, stage, race/ethnicity, marital status, treatment and sequence number.

[c] Multivariate Cox Proportional Hazard Analyses were adjusted for PR status, age, stage, race/ethnicity, marital status, treatment and sequence number.

[d] Multivariate Cox Proportional Hazard Analyses were adjusted for ER status, age, stage, race/ethnicity, marital status, treatment and sequence number.

FIGURES

Figure 1. Figure of Exclusion on Study Cohort

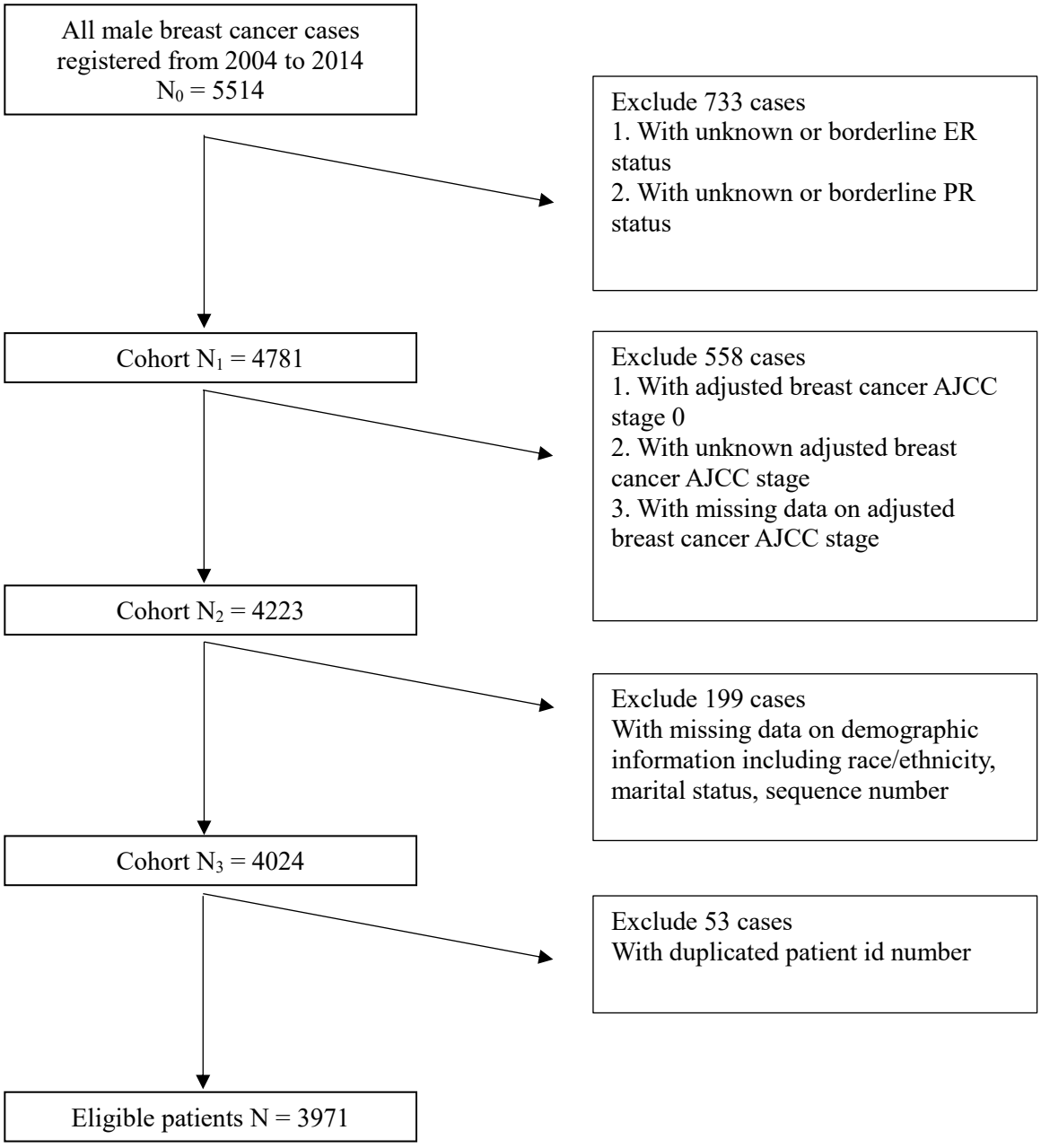


Figure 2. Male Breast Cancer Incidence Trend by Year of Diagnosis in 2004-2014

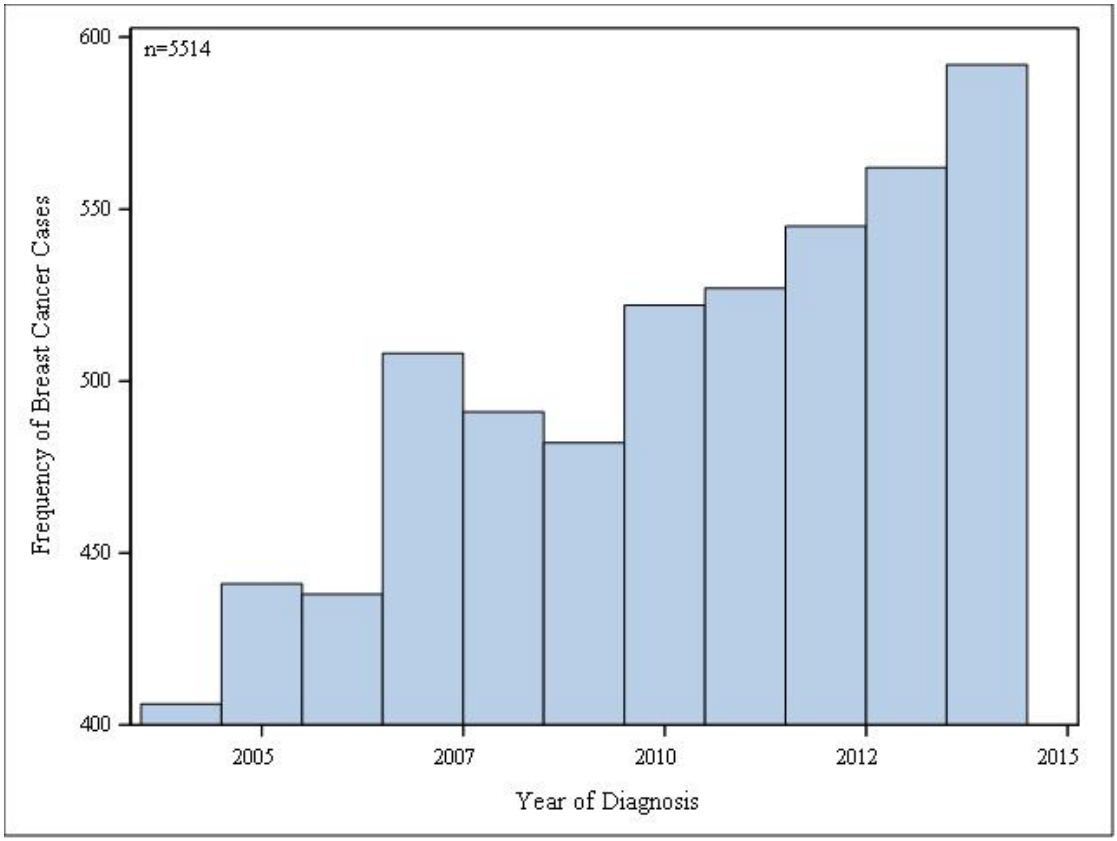


Figure 3. Age-adjusted Rate of Male Breast Cancer in 2004-2014

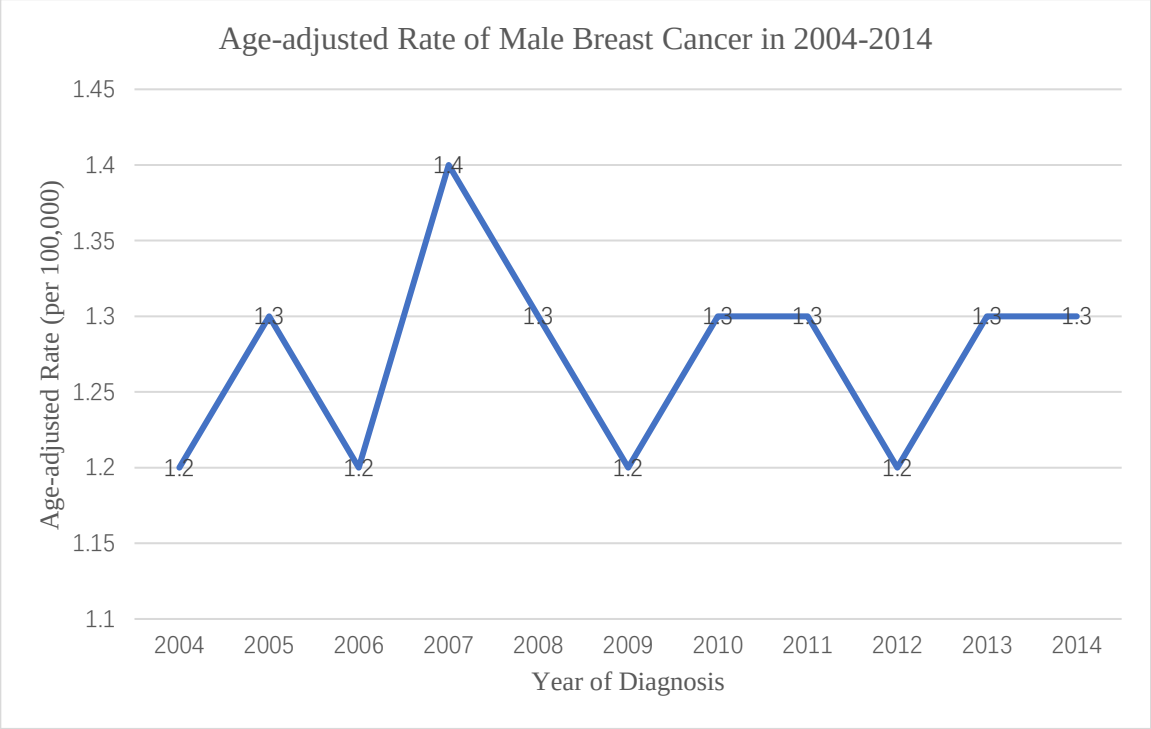
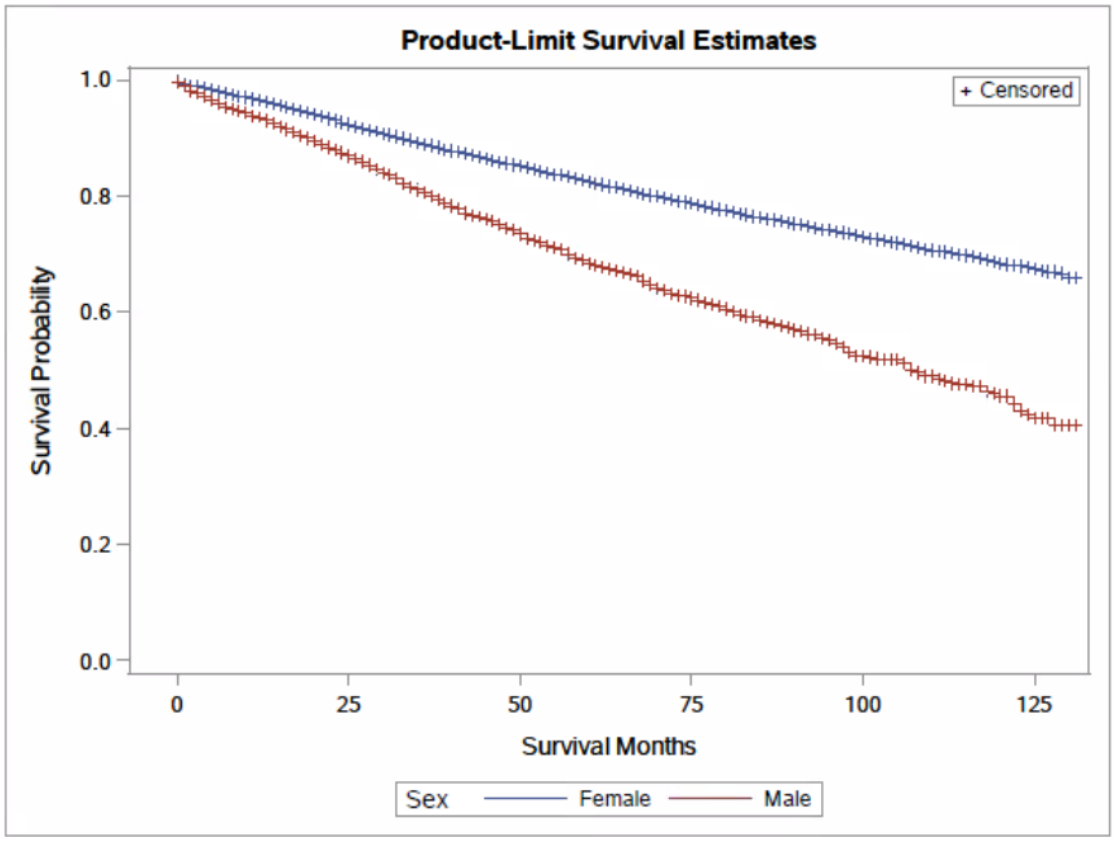


Figure 4. Crude Kaplan-Meier Curve for the Overall Survival of Male and Female Breast Cancer (Log-rank Test: P < .001)



Chapter III

SUMMARY

In this study, there was no significant difference in the 10-year survival of breast cancers which were diagnosed in late stages (III and IV) in each hormone receptor strata. For ER-positive and PR-positive patients, there existed strong differences in the MBC and FBC outcomes in early stage, especially stage II. However, results for ER-negative and PR-negative patients were not significant because almost all male patients were receptor positive. More studies are needed to explore the characteristics of receptor-negative patients. In this study, the survival analysis was based on all-

cause death instead of death due to breast cancer. Future work should look for survival analysis that focus on specific-cause death to further explore the hazard ratio of breast cancer outcomes.