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Breast Cancer Res Treat. 2015 Oct;153(3):679-87.

which has been published in final form at

https://doi.org/10.1007/s10549-015-3582-1

Padron-Monedero A, Koru-Sengul T, Tannenbaum SL, Miao F, Hansra D, Lee D, Byrne MM. Smoking and survival in MALE breast cancer patients. *Breast Cancer Research and Treatment*. 2015;153 (3): 679-87. Impact Factor: 4.085 (D1) (doi: https://doi.org/10.1007/s10549-015-3582-1)

SMOKING AND SURVIVAL IN MALE BREAST CANCER PATIENTS

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Word count: 3148

Key words: Male breast cancer, smoking, survival, health inequalities.

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Abstract

Purpose: To assess whether smoking affects survival in male breast cancer patients for the overall population and when stratified by race, ethnicity and socioeconomic status.

Methods: Data were obtained by linking the 1996-2007 Florida Cancer Data System (FCDS), the Florida Agency for Health Care Administration (AHCA), and the US Census. Inclusion criteria were males ≥18 years, diagnosed with breast cancer and residing in Florida (n=1,573). To analyze the association between smoking and survival, we performed sequential multivariate Cox proportional hazards regression models with progressive adjustment for main confounders.

Results: Compared to never smokers, worse survival was found in current (hazard ratio=1.63; 95% CI=1.23-2.16) but not in former smokers (1.26; 0.99-1.59). Those who smoked ≥1 packs/day had worse survival (2.48; 1.59-3.87) than never smokers with a significant dose-response (p for linear trend<0.001). Race-ethnic stratified models comparing current and former smokers with never smokers found significant differences among Whites [(1.88; 1.44-2.44) and (1.31; 1.04-1.65, respectively)] and non-Hispanics, [(1.73; 1.31-2.28) and (1.31; 1.04-1.66, respectively)].

Conclusions: Overall, current smokers were found to have significantly reduced survival, which was worse by intensity of smoking. Also, any smoking history is associated with worse survival in White and non-Hispanic male breast cancer patients compared to never smokers. Thus, male breast cancer patients should be advised to quit smoking.

Abbreviations. SES: Socioeconomic status; FCDS: Florida Cancer Data System; AHCA: Agency for Health Care Administration; HR: Hazard ratio; CI: Confidence interval; CA: Carcinoma.

INTRODUCTION

The association between smoking and male breast cancer survival has never been examined. The possible relation between smoking and male [1,2] and female breast cancer incidence is complex and most of the data comes from female studies [3]. This is likely due to the fact that male breast cancer is a relatively rare disease. In 2011 the age-adjusted incidence rates overall and for White, Black and Hispanic males were 1.4, 1.3, 1.9 and 0.8 per 100,000 respectively, while the age-adjusted mortality rates of these same groups were 0.3, 0.3, 0.5 and 0.2 per 100,000 respectively [4]. Although, disparities in survival have been shown in female breast cancer by race, ethnicity, and socioeconomic status (SES) [5], only a limited number of studies analyzed those disparities on male breast cancer patients.

Female and male breast cancers have major differences in terms of incidence, racial and age-frequency distribution [6]. Also some prognostic factors differ when comparing males with premenopausal females [6], so the two sexes may not share similar pathophysiologic drivers of carcinogenesis. Thus, studies in male breast cancer patients are needed to identify male-specific risk factors of incidence and survival. Moreover, different characteristics in some prognostic factors have been proved between White and Black male breast cancer patients (Black males have larger tumor size, more positive nodes, higher nuclear grade and a lower positive to negative receptor expression than Whites) [6]. But as far as we know there are no studies that assessed the possible association between risk behaviors and male breast cancer survival for the different racial subpopulations. Our group has previously found that smoking was associated with an increased risk of mortality in female breast cancer patients with a linear dose-response after adjustment for socio-demographic, clinical-pathological variables, and co-morbidities [7]. Thus, we first aimed to determine if smoking status and intensity is also associated with survival in male breast cancer patients after adjustment for known confounders (including co-morbidities and stage at presentation); and second, we aimed to assess whether there is a difference in this association by race, ethnicity, and SES.

METHODS

Study design and population

Data were obtained by linking the Florida Cancer Data System (FCDS), the Florida Agency for Health Care Administration (AHCA), and the US Census to form an extensive dataset of Floridian men diagnosed with breast cancer from 1996-2007. In the state of Florida and as required by law, the FCDS is a population based registry that collects information on cancer patient socio-demographics, diagnosis (ICD-9 codes), clinico-pathological and therapeutic data. Approximately 95% of all incident cases of cancer in Florida are captured. The AHCA database captures every patient encounter occurring in Florida hospitals, and free standing ambulatory surgical and radiation clinics, which provides additional information about diagnosis and procedures. We used de-identified data to protect patient confidentiality.

Inclusion criteria were male patients who were diagnosed with breast cancer in the state of Florida during the years 1996-2007 (n=2,111). Patients younger than 18 years old, with carcinoma-in-situ and non-Florida residents were excluded (n=375). Patients with missing values for race, ethnicity and SES were excluded from the analysis (n=145), and we also excluded patients from races other than Black and White due to their small sample size (n=18 or 1% of the sample) resulting in a total analytical sample size of 1,573.

Because of the large number of patients of unknown smoking status (23.5% of the sample), we did not exclude these patients to avoid bias in our results because it is possible that the unknown/missing smoking status cases are fundamentally different from cases for which status is known. For example, cases that are missing cancer registry data are typically Black and more impoverished [8], and those factors could be associated with a worse survival.

Study variables

Overall survival, the primary outcome variable, was defined as time from diagnosis to death or last treatment encounter. We followed the cohort for an additional 3 year period until 2010 to more fully capture survival.

The patients self-reported their smoking status as never, former, current (any frequency of smoking) or unknown smoker at the time of diagnosis. For a subsequent analysis we also classified smokers by intensity: never, <1 packs/day, and ≥1 packs/day.

The main socio-demographic variables of interest were race (White, Black), ethnicity (Hispanic or non-Hispanic), and SES. SES was categorized from US Census information on percent of households at the tract level living below the federal poverty line, with groups defined by: lowest (≥20% below the poverty line), middle-low (≥10% and <20%), middle-high (≥5% and <10%), or highest SES (<5%). Other socio-demographic variables included age at diagnosis, presented as a categorical variable for descriptive purposes (<40, 41-50, 51-65 or >65 years) and used in the regression models as a continuous variable, and marital status (never married, married, divorced/separated/widowed, or unknown). Patients were considered to be obese if their body mass index (BMI) (calculated as weight in kilograms divided by squared height in meters) was >30. Obesity, alcohol abuse, and the rest of the Elixhauser Index co-morbidities (congestive heart failure, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension uncomplicated, hypertension complicated, paralysis, other neurological disorders, chronic pulmonary disease, diabetes uncomplicated, diabetes complicated, hypothyroidism, renal failure, liver disease, peptic ulcer disease excluding bleeding, AIDS, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis collagen vascular disease, coagulopathy, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemia, drug abuse, psychoses and depression) [9] were categorized as yes, no or unknown. As obesity and alcohol abuse could be specifically related to possible breast cancer survival, we presented them as independent variables in Table 2 to stress their importance. The rest of Co-morbidities (excluding obesity and alcohol abuse) were summed as an aggregated variable called "Co-morbidities" and coded as 0, 1-2, 3-4 or >4 for descriptive purposes.

The cancer stage at diagnosis was categorized as 1) localized, 2) regional direct extension with or without lymph node involvement, 3) regional lymph node involvement only, 4) distant metastasis, or 5) unknown or unstaged according to the Surveillance, Epidemiology, and End Results (SEER) Program's summary stage 2000 or 1977. We used by default the SEER 2000 classification and only applied the SEER 1977 classification when we encountered missing data for the former classification.

The histology of the tumor was obtained from the database and divided into the following categories "Carcinoma (CA) ductal", "CA lobular", and "Other" which included the rest of the histologic diagnoses provided. Differentiation grade was classified as "well differentiated", "moderately differentiated", "poorly differentiated", "undifferentiated", or "unknown".

The Estrogen Receptor (ER) and Progesterone Receptor (PR) status were both classified as "positive", "negative" or "unknown" and the treatments (chemotherapy, radiation therapy, surgery, hormonal treatment) were all classified as "yes", "no", or "unknown". The Human Epidermal Growth Factor Receptor 2 (HER-2) status was not collected by FCDS during our study years and thus we were not able to include this factor in our analyses.

Statistical Analyses

The association between categorical variables was examined using Chi-square tests. Log-rank tests were used to examine the unadjusted association of smoking status and overall survival in male breast cancer patients. Cox proportional hazards regressions were used to calculate hazard ratios controlling for confounders.

We constructed four block sequential Cox regression models with smoking status as our main predictor variable. These sequential models were: (1) univariate model (Model A); (2) multivariate model adjusting for all socio-demographic variables, including age, race, ethnicity, SES and marital status (Model B); (3) Model B plus tumor stage, histology, differentiation grade, ER/PR status, chemotherapy, radiation, surgery, and hormonal treatment (Model C); (4) Model C plus obesity, alcohol abuse, and the rest of the individual Elixhauser co-morbidities (Model D). We examined and found no interactions for smoking and race, smoking and ethnicity and smoking and SES in the models.

As the fully adjusted model (Model D) showed that current smokers had a significantly increased risk compared to never smokers, we replicated the sequential models to assess the association between survival and smoking intensity (<1pack/day, ≥1 pack/day in current smokers) using those who never smoked as the reference group. We also calculated the P for linear trend for smoking intensity and survival in breast cancer patients.

Finally, to assess the association between smoking status and survival in male breast cancer patients for different subpopulations, we stratified our sample by race (White, Black), ethnicity (Hispanic or non-Hispanic), and SES (lowest, middle-low, middle-high, highest) and re-analyzed each fully adjusted model separately. In these fully adjusted models, we included the variables obesity, alcohol abuse; however, due to small sample sizes in some of

the subpopulations, the other Elixhauser co-morbidities were summed and included as an aggregated variable (0,1-2,3-4,>4) in the analysis.

Because patients being treated at the same facility are not independent observations due to clustering at the facility level, we used robust standard errors for all analyses. Statistical significance was assessed at $p \leq 0.05$. The SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC) was used to perform all analyses. The study was approved by the Institutional Review Boards of the University of Miami and the Florida Department of Health.

RESULTS

Demographics: The demographic characteristics of male breast cancer cases by self-reported smoking status are depicted in Table 1. Of the 1,573 patients included in the analysis 91.5% were White and 8.5% Black, and the average age at diagnosis was 66.8 years. The average follow-up was 4 years with a range of 0 to 14.1 years. During the course of the study, 35% of the patients of our sample (551 patients) died.

There was a larger proportion of Blacks (44.8%) compared to Whites (39.5%) who were never smokers. A greater percent of Hispanic patients (55%) were never smokers than non-Hispanics (38.5%). A majority of patients in the highest SES were former smokers (26.4%) compared with the percent of former smokers in the lowest SES category (19.3%)

Clinical factors: The clinical characteristics of male breast cancer patients are presented in Table 2. A higher proportion of the patients that were alcohol abusers were current smokers (35.4%) compared to the non-alcohol abusers (10.7%). Former or current smokers were more likely to have greater that 4 co-morbid conditions, moreover, current smokers more frequently presented with distant disease at the time of diagnosis. Of those patients with no comorbid conditions, 41.2% were never smokers and 10.3% were current smokers.

Cox regressions - Smoking status: Cox proportional hazard regression model results by smoking status are given in Table 3 (Smoking Status). In the univariate model, worse survival was found for current and former smokers compared to never smokers [(HR=1.49; 95% CI=1.13-1.95) and (1.62; 1.32-1.99, respectively)]. Progressive adjustment from Model B (adjusted for age, race, ethnicity, SES and marital status) to Model C (additionally

adjusted for SEER, histology, differentiation grade, ER, PR, Chemotherapy, Radiation Therapy, Surgery and Hormonal Treatment) changed the HR for current smokers compared to never smokers [(1.85; 1.42-2.42) and (1.80; 1.36-2.39, respectively)], and for former smokers [(1.52; 1.24-1.85) and (1.39; 1.12-1.73, respectively)]. In the fully-adjusted model, Model D (after additionally adjusting for co-morbidities, current smokers maintained worse survival (1.63; 1.23-2.16) but former smokers no longer displayed significantly worse survival (1.26; 0.99-1.59)) compared to those who never smoked.

In the fully adjusted model D (data not shown), compared to Whites, Blacks have worse survival (2.44; 1.31-4.53). We did not find survival differences between Hispanic and non-Hispanic males (0.70; 0.42-1.16). Likewise, compared to those in the lowest SES category, individuals from the middle-low, middle-high, and highest SES did not have a significantly better survival [(1.03; 0.62-1.69) and (1.01; 0.58-1.76) and (0.99; 0.57-1.73 respectively)] (data not shown).

Cox regressions – Smoking intensity: In an analysis restricted to current and never smokers, we determined the effect of smoking intensity (Table 3; Smoking Intensity). The fully adjusted model, revealed that those who smoked ≥1 packs/day were nearly 2.5 times less likely to survive compared with never smokers (2.48; 1.59-3.87), and there was a significant linear dose response (p for linear trend <0.001)

Cox regressions – Stratified by race, ethnicity and SES: In the stratified analysis using fully adjusted Cox models (Table 4), we found that Whites who were current or former smokers had worse survival compared with never smokers, [(1.88; 1.44-2.44) and (1.31; 1.04-1.65, respectively)]. Current and former Non-Hispanic smokers also had worse survival compared with non-Hispanic never smokers [(1.73; 1.31-2.28) and (1.31; 1.04-1.66, respectively)]. Because of a small sample size, the confidence intervals were very wide for the Hispanic subpopulation [compared to never smokers, worse survival was found in current (hazard ratio=98.84; 95% CI=7.95-1228.66) but not in former smokers (8.57; 0.50-147.33)], thus the results may not be reliable.

Smoking associations were not significant for Blacks. Compared to never smokers, worse survival was observed for current smokers in the highest (2.75; 1.36-5.55), and middle-low SES groups (2.09; 1.18-3.71)

DISCUSSION

This study provides the first known evidence that male breast cancer patients who currently smoke have a worse survival than never smokers, and that there is a significant linear dose-response of smoking intensity. The association of current smoking with survival remains significant after adjusting for numerous potentially confounding factors, including demographic, clinic-pathologic characteristics, treatments and extensive co-morbidities. This association is also significant for Whites and non-Hispanics.

Our results are consistent with the relationship between smoking and survival in female breast cancer patients [7, 10-15]. A large number of factors have been controlled to assess the association between smoking and worse survival. In female breast cancer patients, it has been shown that smokers tend to have more co-morbidities which has a negative impact on female breast cancer survival [3, 16, 17]. Also female smokers have more advanced disease than non-smokers [18]. Our male patients´ survival risk in relation to smoking decreases with progressive adjustment for clinical characteristics and co-morbidities, which is consistent with the results obtained for female breast cancer patients [7]. Lack of adjustment of those variables would have overestimated the impact of current smoking on the mortality of male and female [7] breast cancer patients. However, despite these adjustments, smokers continued to have reduced survival relative to never smokers.

We found an inverse association of survival with smoking intensity; that is, there was a higher dose response to larger quantities of smoking in male breast cancer patients which remained significant in the fully adjusted model. Those smoking 1-pack/day or more had a 148% worse survival after controlling for co-morbidities and all other demographic and clinical characteristics. This inverse association between smoking intensity and survival has also been found in female breast cancer patients [7].

The mortality risk of breast cancer patients in relation to smoking is significant for both sexes, but compared to the study of Padron-Monedero *et al.* [7] appears to be higher for males than for females. This is evident for current smokers (1.63; 1.23-2.16) for males and (1.33; 1.28-1.38) for females [7] compared to never smokers. Also smoking ≥1 pack/day is associated with higher HR for males (2.48; 1.59, 3.87) than for females (1.40; 1.33-1.47 for 1-2 packs/day and 1.70 ;1.45, 1.99 for >2 packs/day) [7]. Therefore, smoking could have more of an impact on male breast cancer survival than on female survival. This gender differences could be partially explained by the fact that

males smoke with more intensity (more deeply and more of each cigarette) and also start smoking at an earlier age than females [19].

We found no significant association between smoking status and survival among Black male breast cancer patients, which is consistent with our study conducted among female breast cancer survivors [7]. Our results, both in males and females, suggest a different susceptibility for breast cancer survival in relation to smoking for the different races. As we have previously suggested for the female breast cancer patients, a greater understanding of differences in underlying genetic and molecular pathways across race and sexes may help provide a better understanding of the underlying relationship between smoking and breast cancer survival, and may explain our findings of racial differences both for males and females [7]. This is consistent with the most recent report by the Surgeon General that states that future research should explore the risk of smoking on breast cancer in genetically defined subgroups [3] as it is possible that the associations between risk for breast cancer and smoking could differ according to different phenotypes. A possible modification of the risk for breast cancer incidence in relation to smoking for the NAT2 genotype has been already suggested [3]. Our results previously in females [7] and in this study in males could be consistent with this line of research in terms of breast cancer survival.

Our results do not show a clear pattern of association between smoking and survival in male breast cancer patients by neighborhood SES. From the stratified models we obtained that only current smokers from the highest and middle-low SES categories had worse survival then their never smoking counterparts. Further studies with a larger sample size should confirm these findings. By contrast, in female breast cancer patients, worse survival with smoking was observed in patients from all neighborhood SES categories [7].

Limitations

We did not have access to HER information which limited our ability to assess a possible relationship between smoking and both HER-2 receptor and triple negative breast cancers on survival. In addition, the number of men with unknown ER and PR status was very high, as little information on either status was collected by FCDS prior to 2004. We assessed smoking status at diagnosis, so we cannot be certain whether quitting after diagnosis would benefit the patient's prognosis. Furthermore, we did not have the length of quit time for former smokers. However, both male and female [7] current smokers appear to have a worse prognosis than former smokers, so the effect of

smoking on survival decreases after quitting smoking regardless of how long prior to diagnosis the patient quit. Next, smoking status was self-reported, so we expect to have some response bias [20]. Some of our stratified analysis had a lack of statistical power due to our limited numbers of male breast cancer patients. It is also possible that potential gender misclassification may had occurred [21]. Finally, these findings may not be representative of all male breast cancer patients from states other than Florida.

Strengths

The notable strength of our study is that although our sample size was small, it is the largest known study of male breast cancer patient survival by smoking status, race, ethnicity, and SES while controlling for other prognostic factors. We were therefore able to identify the independent effect of smoking on breast cancer patients' survival and also to assess the dose-response.

CONCLUSIONS

Smoking is consistently associated with an increased risk of mortality in most populations of male breast cancer patients with a linear dose-response. Although white males may benefit most, smoking cessation should be promoted, as part of the tertiary prevention protocols, for all male breast cancer patients. Future studies should analyze the possible mechanisms of the differential risk of smoking on survival for the different races and genders.

COMPLIANCE WITH ETHICAL STANDARDS

This manuscript complies with the current laws of the country in which the research was performed. The study was approved by the Institutional Review Boards of the University of Miami and the Florida Department of Health in the US, and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

ACKNOWLEDGMENTS

This study was funded by the James & Esther King Florida Biomedical Research Program (Grant 10KG-06).

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1) Ewertz M1, Holmberg L, Tretli S, Pedersen BV, Kristensen A (2001). Risk factors for male breast cancer--a case-control study from Scandinavia. *Acta Oncol* 40(4):467-71.

2) Hsing AW, McLaughlin JK, Cocco P, Co Chien HT, Fraumeni JF Jr (1998). Risk factors for male breast cancer (United States). *Cancer Causes Control* 9(3):269-75.

3) US Department of health and human services (2014). The Health Consequences of Smoking. 50 years of Progress: A report of the surgeon general. http://www.cdc.gov/tobacco/data_statistics/sgr/50th-anniversary/index.htm#report .Accessed 10 October 2014.

4) US Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute U.S. Cancer Statistics Working Group (2014). United States Cancer Statistics: 1999–2011 Incidence and Mortality Web-based Report. www.cdc.gov/uscs .Accessed 28 February 2015.

5) Tannenbaum SL, Koru-Sengul T, Miao F, Byrne MM (2013). Disparities in survival after female breast cancer diagnosis: a population-based study. *Cancer Causes and Control*.24 (9):1705-1715. doi: 10.1007/s10552-013-0246-5.

6) Anderson WF, Althuis MD, Brinton LA, Devesa SS (2004). Is male breast cancer similar or different than female breast cancer? *Breast Cancer Res Treat* 83(1):77-86.

7) Padron-Monedero A, Tannenbaum SL, Koru-Sengul T, Miao F, Hansra D, Lee DJ, Byrne MM (2015). Smoking and survival in female breast cancer patients. *Breast Cancer Res Treat*. 150(2): 395-403. doi:10.1007/s10549-015-3317-3.

8) Boscoe FP, Sherman C (2006). On Socioeconomic Gradients in Cancer Registry Data Quality (letter) *Journal Epidemiology Community Health* 60:551.

9) Elixhauser A1, Steiner C, Harris DR, Coffey RM (1998). Comorbidity measures for use with administrative data. *Med Care.* 36(1):8-27.

10) Calle EE, Miracle-McMahill HL, Thun MJ, Heath CW (1994). Cigarette smoking and risk of fatal breast cancer. *Am J Epidemiol* 139(10):1001-7.

11) Holmes MD, Murin S, Chen WY, Kroenke CH, Spiegelman D, Colditz GA (2007). Smoking and survival after breast cancer diagnosis. *Int J Cancer* 120(12):2672-7.

12) Hellmann SS, Thygesen LC, Tolstrup JS, Gronbaek M (2010). Modifiable risk factors and survival in women diagnosed with primary breast cancer: results from a prospective cohort study. *Eur J Cancer Prev* 19(5):366-73.doi: 10.1097/CEJ.0b013e32833b4828.

13) Manjer J, Andersson I, Berglund G, Bondesson L, Garne JP, Janzon L, Malina J, Matson S (2000). Survival of women with breast cancer in relation to smoking. *Eur J Surg* 166(11):852-8.

14) Yu GP, Ostroff JS, Zhang ZF, Tang J, Schantz SP (1997). Smoking history and cancer patient survival: a hospital cancer registry study. *Cancer Detect Prev* 21(6):497-509.

15) Wojcik BE, Spinks MK, Optenberg SA (1998). Breast carcinoma survival analysis for African American and white women in an equal-access health care system. *Cancer* 82(7):1310-8.

16) Land LH, Dalton SO, Jorgensen TL, Ewertz M (2012). Comorbidity and survival after early breast cancer. A review. *Crit Rev Oncol Hematol* 81(2):196-205. doi: 10.1016/j.critrevonc.2011.03.001.

17) Satariano WA. Aging, comorbidity, and breast cancer survival: an epidemiologic view (1993). *Adv Exp Med Biol* 330:1-11.

18) Daniell HW (1988). Increased lymph node metastases at mastectomy for breast cancer associated with host obesity, cigarette smoking, age, and large tumor size. *Cancer* 62(2):429-435.

19) Zang EA, Wynder EL (1996). Differences in lung cancer risk between men and women: examination of the evidence. *Journal of the National Cancer Institute* 88:183-192.

20) Woodward M, Tunstall-Pedoe H (1992). Biochemical evidence of persistent heavy smoking after a coronary diagnosis despite self-reported reduction: analysis from the Scottish Heart Health Study. *Eur Heart J* 13(2):160-5.

21) Sherman RL, Boscoe FP, O'Brien DK, George JT, Henry KA, Soloway LE, Lee DJ (2014). Misclassification of sex in central cancer registries. *J Registry Manag*. 41(3):120-4.

Table 1: Demographics Characteristics of Male Breast Cancer Patients in Florida by smoking status using linked datasets from the Florida Comprehensive Data System, the Agency for Health Care Administration, and the US Census (1996-2007)

	All		Smoking status							
			Never		Former		Current		Unknown	
	n	col%[b]	n	row%	n	row%	n	row%	n	row%
Total sample	1,573	100	629	40	391	24.9	184	11.7	369	23.5
Deaths	551	35.0	191	34.7	170	30.9	76	13.8	114	20.7
Age at diagnosis (yrs)										
Mean (SD)	66.8 (13.7)		66.5 (14.0)		70.6 (12.0)		61.3 (12.3)		65.9 (14.5)	
Median (25^{th}%, 75^{th}%)	69.0 (57, 77)		69.0 (56, 77)		72.0 (64, 79)		61.5 (51, 71)		68.0 (56, 77)	
min, max	25, 100		26, 97		27, 100		31, 86		25, 96	
Age at diagnosis (yrs)										
<40	60	3.8	23	38.3	8	13.3	8	13.3	21	35.0
41-50	164	10.4	75	45.7	20	12.2	31	18.9	38	23.2
51-65	446	28.4	180	40.4	83	18.6	74	16.6	109	24.4
>65	903	57.4	351	38.9	280	31.0	71	7.9	201	22.3
Race										
White	1,439	91.5	569	39.5	371	25.8	167	11.6	332	23.1
Black	134	8.5	60	44.8	20	14.9	17	12.7	37	27.6
Hispanic origin										
No	1,433	91.1	552	38.5	374	26.1	168	11.7	339	23.7
Yes	140	8.9	77	55.0	17	12.1	16	11.4	30	21.4
SES[a]										
Lowest	171	10.9	72	42.1	33	19.3	23	13.5	43	25.1
Middle-low	457	29.1	178	38.9	108	23.6	55	12.0	116	25.4
Middle-high	615	39.1	249	40.5	163	26.5	68	11.1	135	22.0
Highest	330	21.0	130	39.4	87	26.4	38	11.5	75	22.7
Marital status										
Never Married	193	12.3	70	36.3	37	19.2	29	15.0	57	29.5
Married	1,029	65.4	432	42.0	264	25.7	112	10.9	221	21.5
Divorced/Separated/Widowed	304	19.3	112	36.8	82	27.0	40	13.2	70	23.0
Unknown	47	3.0	15	31.9	8	17.0	3	6.4	21	44.7

[a] SES: Socioeconomic status: percent of households at the tract level living below the federal poverty line: lowest (≥20%), middle-low (≥10% and <20%), middle-high (≥5% and <10%), and highest (<5%).

[b] Only the "ALL" column is displayed by column percent.

Table 2: Clinical Characteristics of Male Breast Cancer Patients in Florida by smoking status using linked datasets from the Florida Comprehensive Data System, the Agency for Health Care Administration, and the US Census (1996-2007)

	All		Smoking status							
			Never		Former		Current		Unknown	
	n	col%[b]	n	row%	n	row%	n	row%	n	row%
Co-morbidities[a]										
None	165	10.5	68	41.2	35	21.2	17	10.3	45	27.3
1-2	376	23.9	166	44.1	67	17.8	39	10.4	104	27.7
3-4	364	23.1	155	42.6	91	25.0	39	10.7	79	21.7
>4	668	42.5	240	35.9	198	29.6	89	13.3	141	21.1
Obesity										
Yes	173	11.0	75	43.4	35	20.2	24	13.9	39	22.5
No	1235	78.5	486	39.4	321	26	143	11.5	285	23.1
Unknown	165	10.5	68	41.2	35	21.2	17	10.3	45	27.3
Alcohol abuse										
Yes	65	4.1	14	21.5	17	26.2	23	35.4	11	16.9
No	1343	85.4	547	40.7	339	25.2	144	10.7	313	23.3
Unknown	165	10.5	68	41.2	35	21.2	17	10.3	45	27.3
SEER										
Localized	761	48.4	321	42.2	187	24.6	81	10.6	172	22.6
Regional, direct extension ± lymph nodes	167	10.6	63	37.7	56	33.5	13	7.8	35	21.0
Regional, lymph nodes only	352	22.4	159	45.2	77	21.9	49	13.9	67	19.0
Distant	96	6.1	30	31.3	27	28.1	21	21.9	18	18.8
Unknown	197	12.5	56	28.4	44	22.3	20	10.2	77	39.1
Histology										
Ductal CA	1172	74.5	469	40	304	25.9	143	12.2	256	21.8
Lobular CA	103	6.5	51	49.5	16	15.5	12	11.7	24	23.3
Other	298	18.9	109	36.6	71	23.8	29	9.7	89	29.9
Grade										
Well-differentiated	161	10.2	68	42.2	35	21.7	25	15.5	33	20.5
Moderately differentiated	611	38.8	249	40.8	156	25.5	71	11.6	135	22.1
Poorly-differentiated	393	25.0	160	40.7	104	26.5	47	12.0	82	20.9
Undifferentiated	21	1.3	11	52.4	4	19.0	4	19.0	2	9.5
Unknown	387	24.6	141	36.4	92	23.8	37	9.6	117	30.2
ER Status										
Positive	444	28.2	191	43	119	26.8	53	11.9	81	18.2
Negative	57	3.6	22	38.6	14	24.6	10	17.5	11	19.3

	All		Smoking status							
			Never		Former		Current		Unknown	
	n	col%[b]	n	row%	n	row%	n	row%	n	row%
Unknown	1072	68.2	416	38.8	258	24.1	121	11.3	277	25.8
PR Status										
Positive	380	24.2	161	42.4	101	26.6	49	12.9	69	18.2
Negative	113	7.2	48	42.5	29	25.7	13	11.5	23	20.4
Unknown	1080	68.7	420	38.9	261	24.2	122	11.3	277	25.6
Chemotherapy										
Yes	376	23.9	151	40.2	97	25.8	55	14.6	73	19.4
No	1109	70.5	444	40.0	275	24.8	120	10.8	270	24.3
Unknown	88	5.6	34	38.6	19	21.6	9	10.2	26	29.5
Radiation Therapy										
Yes	416	26.4	161	38.7	116	27.9	68	16.3	71	17.1
No	1113	70.8	455	40.9	272	24.4	111	10.0	275	24.7
Unknown	44	2.8	13	29.5	3	6.8	5	11.4	23	52.3
Surgery										
Yes	1495	95.0	612	40.9	371	24.8	174	11.6	338	22.6
No	60	3.8	15	25.0	18	30.0	9	15.0	18	30.0
Unknown	18	1.1	2	11.1	2	11.1	1	5.6	13	72.2
Hormonal Treatment										
Yes	252	16.0	113	44.8	84	33.3	27	10.7	28	11.1
No	1237	78.6	490	39.6	292	23.6	144	11.6	311	25.1
Unknown	84	5.3	26	31.0	15	17.9	13	15.5	30	35.7

[a] Co-morbidities: aggregated variable by summing all Elixhauser Comorbidity Index except obesity and alcohol abuse.
[b] Only the "ALL" column is displayed by column percent.

Table 3: Cox Proportional Hazard Regression Models for Overall Survival in male Breast Cancer by smoking status and smoking intensity (packs/day)

	Model A		**Model B**		**Model C**		**Model D**	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Smoking Status								
Never	1		1		1		1	
Current	1.49 (1.13, 1.95)	<0.004	1.85 (1.42, 2.42)	<0.001	1.80 (1.36, 2.39)	<0.001	1.63 (1.23, 2.16)	<0.001
Former	1.62 (1.32, 1.99)	<0.001	1.52 (1.24, 1.85)	<0.001	1.39 (1.12, 1.73)	0.003	1.26 (0.99, 1.59)	0.056
Unknown	1.12 (0.81, 1.54)	0.492	1.11 (0.80, 1.54)	0.531	0.96 (0.71, 1.29)	0.792	0.89 (0.68, 1.16)	0.373
Smoking Amount (pack/day)								
Never	1		1		1		1	
<1	1.24 (0.73, 2.08)	0.428	1.48 (0.82, 2.68)	<0.190	1.39 (0.87, 2.24)	0.172	1.11 (0.60, 2.06)	0.743
≥1	1.83 (1.31, 2.55)	<0.001	2.28 (1.63, 3.17)	<0.001	2.47 (1.79, 3.39)	<0.001	2.48 (1.59, 3.87)	<0.001
P linear trend		0.001		<0.001		<0.001		<0.001

Model A: Univariate: smoking only
Model B: Multivariate: smoking+ age, race/ethnicity/SES, marital status
Model C: Multivariate: Model B+ SEER, histology, differentiation grade, ER, PR, Chemotherapy, Radiation Therapy, Surgery, Hormonal Treatment
Model D: Multivariate: Model C+ co-morbidities

Table 4: Cox Proportional Hazard Regression Models for Overall Survival in males with breast cancer by race/ethnicity/SES[a]

Models[b]		Smoking status						
		Never	**Former**		**Current**		**Unknown**	
		Reference	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
	Race							
1	White	1	1.31 (1.04, 1.65)	0.023	1.88 (1.44, 2.44)	<0.001	0.96 (0.71, 1.30)	0.793
2	Black	1	2.67 (0.18, 39.45)	0.475	13.50 (0.85,213.87)	0.065	0.82 (0.16, 4.25)	0.812
	Ethnicity							
3	Non-Hispanic	1	1.31 (1.04, 1.66)	0.024	1.73 (1.31, 2.28)	<0.001	0.88 (0.66, 1.16)	0.363
4	Hispanic	1	8.57 (0.50, 147.33)	0.139	98.84 (7.95,1228.66)	<0.001	4.85 (0.35, 66.33)	0.237
	Socioeconomic Status[c]							
5	Lowest	1	1.64 (0.77, 3.52)	0.203	1.47 (0.47, 4.64)	0.511	0.58 (0.27, 1.24)	0.160
6	Middle-low	1	1.55 (1.00, 2.39)	0.050	2.09 (1.18, 3.71)	0.012	1.29 (0.81, 2.07)	0.279
7	Middle-high	1	1.17 (0.73, 1.87)	0.517	1.63 (0.90, 2.95)	0.104	0.77 (0.42, 1.43)	0.410
8	Highest	1	2.16 (1.09, 4.26)	0.027	2.75 (1.36, 5.55)	0.005	0.60 (0.25, 1.47)	0.268

[a] Please note that each row depicts a separate model.

[b] All models are adjusted by: age at diagnosis, marital status, comorbidities, SEER, histology, differentiation grade, ER status, PR status, chemotherapy, radiation therapy, surgical treatment and hormonal treatment.

Models 1 and 2 are additionally adjusted by Ethnicity and SES.

Models 3 and 4 are additionally adjusted by Race and SES.

Models 5, 6, 7 and 8 are additionally adjusted by Race and Ethnicity.

[c] Socioeconomic Status was categorized from the US Census tract-level information on percent of households in the neighborhood living below the poverty index. Each tract was grouped by lowest (≥20%), middle-low (≥10% and <20%), middle-high (≥5% and <10%), or highest (% <5%).