Body mass index and risk of recurrence and mortality of luminal, triple-negative, and HER2-overexpressing breast cancer

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Abstract

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Breast cancer is a leading cause of death of women worldwide, and there is an understanding that risk factors for breast cancer recurrence and mortality differ by subtype. The most common subtypes are: luminal (estrogen receptor positive and/or hormone receptor positive), estrogen receptor negative and her2-overexpressing (H2E), and triple negative (TN). Overweight and obesity, as measured by body mass index (BMI), has been suspected to be associated with an increased risk of breast cancer recurrence and mortality but results have been inconsistent by subtype. We conducted a longitudinal cohort study to assess the association between BMI and breast cancer recurrence and breast cancer specific mortality (BCSM), stratified by breast cancer subtype using multi-variable adjusted Cox proportional hazards models. Our population consisted of 1,938 luminal (156 recurrences, 173 breast cancer deaths), 686 H2E (59 recurrences, 60 deaths), and 1,193 TN (260 recurrences, 273 deaths) patients. Mean follow up time was 4.1 years for recurrence and 10.4 years for BCSM. Compared to normal weight women, neither overweight nor obesity was associated with a significantly increased risk of recurrence for luminal subtype, (HR=1.15, 95% CI 0.78-1.71 and 1.23, 95% 0.84-1.79, respectively), while obesity (HR= 2.21, 95% CI 1.13-4.32), but not overweight (HR=1.42, 95% CI 0.70-2.88) was associated with recurrence in H2E patients. Overweight (HR=0.61, 95% CI 0.44-0.85) was inversely associated with recurrence in patients with TN breast cancer, while no association was observed for obese patients (HR=0.89, 95% CI 0.67-1.19). The pattern of results by subtype for BCSM was similar to that observed for recurrence. These findings add to the literature on associations between BMI and subtype specific recurrence and mortality

risks and provides further evidence that associations differ by subtype, with moderate to strongly positive associations for obesity in H2E patients, and weaker associations for other subtypes.

Introduction

Breast cancer (BC) recurrence and mortality differ by histologic grade, status of hormone receptors, and human epidermal growth factor receptor 2 (HER2) expression.[1,2] Each BC subtype possesses unique biological features that may respond differently to treatment methods.[3] This makes each patient's subtype important to understand. The three most common subtypes are: luminal, TN (triple negative) and H2E (her2-overexpressing). TN and H2E are aggressive subtypes with a lower 5-year survival rate than luminal BC.[4] This lower survival rate can be compared to luminal tumors, which has a higher survival rate but may exceed the rate of recurrence compared to TNBC patients.[4]

Obesity, typically determined based on a body mass index (weight for height measure) greater than or equal to 30 kg/m^2, is associated with higher risks for developing breast cancer in certain subtypes such as TN.[5] Obesity is hypothesized to increase the risk of breast cancer due to an excess of adipose tissue creating inflammatory cytokines, higher circulating concentrations of estrogen, and an environment that promotes cancer invasion and growth.[4,5] It is also well established that obesity is a risk factor for postmenopausal breast cancer with a 7% increase per $4kg/m^2$ increase in BMI and a 6% increase per 10kg increase in weight.[4]

Overweight and obesity have been associated with an increased risk of recurrence in some studies and consistency of associations vary by subtype. A study that included 6885 patients with a luminal subtype found that compared to patients with a BMI less than 25 kg/m^2, those considered obese had a 40% greater risk of recurrence.[6] However, a different study that included 818 patients with luminal subtypes found no association between BMI and recurrence in luminal patients (HR=1.5, 95% CI 1.0-2.2, p value = 0.07).[7] When considering H2E patients, none of the four studies we found observed a statistically significant association between BMI and breast cancer recurrence.[7-10] Some of these studies may have been underpowered to detect weaker associations, as the number of recurrences ranged from 22 events[8] to 314.[9] For TN patients, three of four[7,9,11,12] studies found no association between obesity and breast cancer recurrence. Because sample sizes were relatively small (range of 418[11] to 3012,[9]), statistical

power is a concern. The fourth study, which included only premenopausal women, found that obesity was associated with a 70% elevated risk of recurrence.[7]

The association between obesity and breast cancer specific mortality (BCSM) was recently studied in a large systematic review and meta-analysis. Pang et al. included 173 studies and a total of 519,544 patients and 25,751 breast cancer specific deaths.[13] Obesity in luminal and H2E patients was associated with 26% (meta-analysis RR=1.26, 95% CI 1.11-1.43) and 34% (meta-analysis RR=1.34, 95% CI 1.05-1.71) higher risks, respectively, for BCSM when compared to patients who were not obese or overweight.[13] This study found no association (meta-analysis RR=1.17, 95% CI 0.92-1.47) for obesity and BCSM in TN patients, possibly due to the limited number of studies (n=10) on BCSM in patients with TN breast cancer.[13]

In summary, these prior studies indicate a possible greater risk of breast cancer recurrence associated with obesity in patients with luminal subtypes and higher risks of BCSM in patients with luminal and H2E subtypes. There is less evidence supporting an elevated risk of recurrence for H2E patients with obesity or an elevated risk of recurrence and BCSM among TN subtypes, though prior studies may have been underpowered. This study aims to better assess the extent to which BMI is associated with breast cancer recurrence and mortality in these three subtypes. This could be helpful for individually tailored treatment and follow-up plans based on subtype of breast cancer, monitoring of possible recurrences, and to prevent loss of quality of life and mortality.

Methods

Study design and population

We conducted a longitudinal cohort study to assess the relationship between BMI, risk of recurrence, and risk of BCSM across the following three subtypes of breast cancers: 1) luminal (estrogen receptor positive or ER+ and/or hormone receptor positive or PR+), 2) estrogen receptor negative and HER2 positive (H2E) and 3) triple negative (ER-/PR-/HER2- or TN). The data for this study were

collected as part of the BRAVO study at the Fred Hutch Cancer Research Center in Seattle, Washington, and was conducted between 2004 and 2015. Eligible participants were women aged 20-69 diagnosed with primary breast cancer between June 1, 2004, and June 30, 2012 in Seattle, Washington and Albuquerque, New Mexico. Patients were identified through the Surveillance, Epidemiology and End Results (SEER) cancer registries serving each of these geographic regions. In New Mexico, participants were recruited through review of medical records under an IRB-approved waiver of consent. No contact was made with study participants. In Seattle, eligible participants were sent a letter explaining the study purpose and procedures, followed by a telephone call several days later from a trained interviewer to obtain verbal consent for an interview and/or access to the patient's medical records.

Subtype of each patient was determined by the study team through medical records and pathology reports. To increase the power of the study, all H2E and TN patients were included. A random sample of approximately 25% of the luminal cases were frequency-matched to TN and H2E patients on diagnosis year and age. In total, 2,383 ER+, 1,559 TN, and 615 H2E cases were enrolled for a sample size of 4,557.

Data collection

Data on selected demographic factors as well as breast cancer subtype, BMI, recurrences, and death were abstracted from medical records by trained staff at the Seattle-Puget Sound and New Mexico Fred Hutch study locations. Additional information was collected only at the Seattle-Puget Sound location via a structured interviewer-administered questionnaire. These interviews and medical record reviews captured data on epidemiologic, demographic, and clinical factors from patients. To ensure consistency between abstraction methods at the two study sites, a random 10% sample of medical record abstracts were exchanged and reviewed by each site. Our measures of interest - BMI, breast cancer recurrence and mortality – were collected and prioritized through medical records. Insurance status, however, was collected from interviews. Medical records were reviewed in the 2 years after diagnosis to determine treatments received during that time.

Exposure

Body mass index was categorized into three groups: less than 25 kg/m^2 (reference group), 25-29.9 kg/m^2 (overweight), and equal to and above 30 kg/m^2 (obese). This was obtained through review of medical records from inpatient visits and interview data was supplemented when medical records were not available.

Outcome

The outcomes of interest were breast cancer recurrence and BCSM. Both were gathered from patient medical records and reports, with linkages to death certificates in the case of BCSM.

Covariates

Covariates of interest to include in our model were collected through medical record abstraction at the New Mexico site and through both medical record abstraction and phone interview data at the Seattle site. Collection via medical records was prioritized as the primary source of data for all patients.

Data analysis

Survival analysis was performed with time to recurrence of breast cancer defined as time from diagnosis date to date of local or distant recurrence or end of study follow-up time (June 30, 2012). Time to BC-specific death was defined as date of diagnosis to date of patient death, last known follow-up time, or date of study truncation. We estimated hazard ratios (HRs) and their 95% confidence intervals (CIs) of BC recurrence and BCSM associated with BMI using Cox proportional hazards models. To check for violations of proportional hazards, Kaplan Meier curves were plotted for recurrence and BCSM and administrative censoring was included at the end of the study follow-up time. Covariates adjusted for were determined a priori based on the literature studying breast cancer recurrence and mortality by subtype, and included age at diagnosis (<40, 40-49, 50-59, 60+), race/ethnicity (Hispanic, non-Hispanic white, Black, Asian/Pacific Islander, Native American), health insurance status (private, uninsured,

insured through Medicaid, insured through Medicare, military or any other public insurance), stage of breast cancer ((I-IV; I-III in recurrence analyses), hormone therapy use as treatment, chemotherapy use as treatment, and surgery and radiation use as treatment (lumpectomy with radiation, total mastectomy, none of the above or other). From this analysis, we excluded 32 patients with unknown markers, patients with missingness on BMI (n= 38), patients diagnosed with stage 4 BC (n=244), and patients with a second recurrence or recurrence due to a different breast cancer than the original diagnosis (n=92). Those with missingness within our covariates as seen in Table 1 were also excluded. We also used a stratified analysis to evaluate whether the association between BMI and breast cancer recurrence and BCSM differs based on family history of breast cancer or by menopausal status, as prior studies indicated a stronger association between obesity and postmenopausal women[7] and breast cancer has been linked to abnormalities in genes shared with family.[14] Those considered "perimenopausal" in Table 1 were not included in our analysis of comparing premenopausal vs menopausal women. This analysis was performed using the software R.[15]

Results

Demographic characteristics of patients are presented in Table 1, categorized by subtype of breast cancer. Across all subtypes, there was a greater proportion of women ages 50-59 at diagnosis and the majority of participants were Non-Hispanic White (at least 77.8% in each subtype category). Women with luminal subtypes were more frequently diagnosed at stage one, premenopausal, had received hormone therapy as treatment (90.3% of luminal patients), and more likely to have had a lumpectomy with radiation compared to women with other subtypes. Patients with H2E subtype were more heavily recruited at the New Mexico study site than other subtypes and were also less likely to have a family history of breast cancer. TN patients were more likely to be at stage two at diagnosis and had the highest proportion of Black patients with 7.8% compared to other subtypes of luminal and H2E at 3.7% and 4.6%

respectively. Additionally, a smaller proportion of luminal patients were treated with chemotherapy compared to approximately 90% of H2E and TN patients.

A summary of the multivariable Cox proportional hazards models for both BC recurrence and BCSM can be found within tables two through seven. The association between overweight and obesity and recurrence of breast cancer in patients with luminal cancer was weakly positive, but not statistically significant. When compared to our reference group of patients with a BMI less than <25kg/m^2, patients in the overweight category were at a 15% higher risk of recurrence (HR=1.15, 95% CI 0.78-1.71) and patients considered obese were at a 23% increased risk of recurrence (HR=1.23 95% CI 0.84-1.79). In H2E patients, after adjustment for confounders, being overweight was associated with 1.42-times the risk of recurrence (95% CI 0.70-2.88) and obesity was associated with over 2 times the risk of recurrence (HR=2.21, 95% CI 1.13-4.32). Contrastingly, both categories of overweight and obese TN patients were inversely associated with recurrence (overweight: HR=0.61, 95% CI 0.44-0.85; obese: HR=0.89, 95% CI 0.67-1.19). Neither overweight (HR=0.97,95% CI 0.66-1.43) nor obesity (HR= 1.13, 95% CI 0.79-1.62) was associated with BCSM in patients with luminal cancer. However, obesity (HR=1.95, 95% CI 1.01-3.77), but not overweight (HR=1.16, 95 CI 0.58-2.35) was associated with BCSM in H2E patients. Among women with TNBC, there was an inverse association between both overweight (HR = 0.72, 95% CI 0.52-0.98) and obesity (HR= 1.02, 95% CI 0.77-1.35) and BCSM compared to normal weight women.

After stratifying by menopausal status, the same associations were presented between overweight and obese luminal and TN patients. However, H2E patients with obesity who were pre-menopausal had a statistically significant HR of 5.03 (95% CI 1.95-13.0). Similar results were produced with BCSM when stratifying by menopausal status, risk for luminal patients remaining almost identical pre (overweight: HR=0.96, 95% CI 0.53-1.71; obese: HR=1.13 ,95% CI 0.62-2.04) and post (overweight: HR=1.01, 95% CI 0.55-1.85; obese: HR=1.16 ,95% CI 0.69-1.96) stratification. Pre-menopausal H2E patients with obesity also presented with an elevated statistically significant risk of BCSM in women considered obese (HR=4.58, 95% CI 1.03-20.4). Risk of BCSM was elevated in TN patients with obesity who were

postmenopausal (HR=1.20, 95% CI 0.81-1.76), but not among TN patients with obesity who were pre-menopausal (HR=0.84, 95% CI 0.52-1.36), though the results were not statistically significant.

When stratifying by family history of breast cancer, among luminal and TN patients, risk of recurrence associated with overweight and obese populations were similar among women with and without a family history of BC. However, H2E patients with obesity and no family history of BC presented with an increased risk of recurrence (HR=3.50, 95% CI 1.53-8.04). HRs mirrored a similar pattern for BCSM, and H2E patients with obesity who had no family history of BC presented with approximately the same increased risk that was seen with recurrence (HR=3.48, 95% CI 1.50-8.06). These results can be found in Tables 2-7.

Discussion

This analysis found an increased yet not statistically significant association among luminal patients considered overweight and obese and BC recurrence that did not differ by menopausal status or family history of BC. The results pointed to an increased risk of recurrence associated with obesity for H2E patients and an inverse relationship between TN patients with obesity and risk of recurrence and mortality. These findings regarding luminal patients were somewhat aligned with previous literature which pointed to an inconsistent association between obesity and BC recurrence. However, previous literature had indicated no association between recurrence and obesity among H2E patients, and no known increased risk for TN patients which this study pointed towards.

These results also indicate no association between luminal patients with obesity and BCSM, an increased association among H2E patients, and an inverse association among TN patients. While we saw positive associations with the population of H2E patients and mortality, these hazard ratios had wide confidence intervals and fewer outcomes. Compared to the other subtypes, H2E had the smallest sample size in both our recurrence and mortality analyses. These findings were consistent with prior studies

which had indicated that BCSM was associated with an increased risk for luminal and H2E patients with obesity, but not for TN patients.

This study has several limitations. BMI is an imperfect measure of adiposity when considering whole body fat percentages and visceral adipose tissue.[16] It does not include the distribution of adipose tissue which studies have shown is key to how it affects the body and the development of distinct characteristics that may be produced because of it.[17] However, while it is imperfect, it does often correlate with relevant adiposity measures that can be helpful to be cognizant of. Additionally, like previously mentioned, we excluded patients who had missingness for covariates, which resulted in lower numbers of recurrence and mortality within the analysis. This may have contributed to our wide confidence intervals, reducing statistical power to detect weak associations. However, a main strength of this study is the relatively large sample size of each breast cancer subtype enrolled in comparison to previous studies.

In conclusion, our results were consistent with some findings in previous literature but also produced associations that were seen in limited numbers previously, suggesting H2E patients who have a BMI classified as obese may be at a higher risk for recurrence and BCSM. As this is one of only a handful of studies that has evaluated these relationships, more research is needed to confirm these results. This research can help to identify steps towards more effective treatment plans and monitoring among breast cancer patients with these subtypes.

References

1. Metzger-Filho, O.; Sun, Z.; Viale, G.; Price, K. N.; Crivellari, D.; Snyder, R. D.; Gelber, R. D.; Castiglione-Gertsch, M.; Coates, A. S.; Goldhirsch, A.; Cardoso, F. (2013). Patterns of Recurrence and Outcome According to Breast Cancer Subtypes in Lymph Node-Negative Disease: Results From International Breast Cancer Study Group Trials VIII and IX. Journal of Clinical Oncology, 31(25), 3083–3090. doi:10.1200/JCO.2012.46.1574

2. Ahmad, A. (2013). Pathways to breast cancer recurrence. *ISRN Oncology*, *2013*, 1–16. https://doi.org/10.1155/2013/290568
3. Yersal O, Barutca S. Biological subtypes of breast cancer: Prognostic and therapeutic implications. World J Clin Oncol. 2014 Aug 10;5(3):412-24. doi: 10.5306/wjco.v5.i3.412. PMID: 25114856; PMCID: PMC4127612.
4. Chen, Lu; Cook, Linda S.; Tang, Mei-Tzu C.; Porter, Peggy L.; Hill, Deirdre A.; Wiggins, Charles L.; Li, Christopher I. (2016). *Body mass index and risk of luminal, HER2-overexpressing, and triple negative breast cancer. Breast Cancer Research and Treatment, 157(3), 545–554.* doi:10.1007/s10549-016-3825-9
5. Picon-Ruiz, M., Morata-Tarifa, C., Valle-Goffin, J. J., Friedman, E. R., & Slingerland, J. M. (2017). Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention. *CA: a cancer journal for clinicians*, *67*(5), 378–397. https://doi.org/10.3322/caac.21405
6. Sparano, J. A., Wang, M., Zhao, F., Stearns, V., Martino, S., Ligibel, J. A., Perez, E. A., Saphner, T., Wolff, A. C., Sledge, G. W., Jr, Wood, W. C., Fetting, J., & Davidson, N. E. (2012). Obesity at diagnosis is associated with inferior outcomes in hormone receptor-positive operable breast cancer. Cancer, 118(23), 5937–5946. https://doi.org/10.1002/cncr.27527
7. Turkoz, F. P., Solak, M., Petekkaya, I., Keskin, O., Kertmen, N., Sarici, F., Arik, Z., Babacan, T., Ozisik, Y., & Altundag, K. (2013). The prognostic impact of obesity on molecular subtypes of breast cancer in premenopausal women. Journal of B.U.ON. : official journal of the Balkan Union of Oncology, 18(2), 335–341.
8. Cantini, Luca; Pistelli, Mirco; Merloni, Filippo; Fontana, Andrea; Bertolini, Ilaria; De Angelis, Claudia; Bastianelli, Lucia; Della Mora, Arianna; Santinelli, Alfredo; Savini, Agnese; Maccaroni, Elena; Diodati, Lucrezia; Falcone, Alfredo; Berardi, Rossana (2019). Body mass index and hormone receptor status influence recurrence risk in HER-2 positive early breast cancer patients. Clinical Breast Cancer, (), S1526820919300813–. doi: 10.1016 / j.clbc.2019.06.008

9. Abubakar, M., Sung, H., Bcr, D., Guida, J., Tang, T. S., Pfeiffer, R. M., & Yang, X. R. (2018). Breast cancer risk factors, survival and recurrence, and tumor molecular subtype: analysis of 3012 women from an indigenous Asian population. Breast cancer research : BCR, 20(1), 114. https://doi.org/10.1186/s13058-018-1033-8
10. Kim, S. W., Chun, M., Jung, Y. S., Oh, Y. T., Noh, O. K., & Cho, O. (2021). Impact of Body Mass Index on Local Recurrence according to Intrinsic Subtype Approximation in Korean Women with Early Stage Invasive Breast Cancer Receiving Contemporary Treatments. Journal of Cancer, 12(15), 4648–4654. https://doi.org/10.7150/jca.59064
11. Ademuyiwa, F. O., Groman, A., O'Connor, T., Ambrosone, C., Watroba, N., & Edge, S. B. (2011). Impact of body mass index on clinical outcomes in triple-negative breast cancer. Cancer, 117(18), 4132–4140. https://doi.org/10.1002/cncr.26019
12. Sun, H., Zou, J., Chen, L., Zu, X., Wen, G., & Zhong, J. (2017). Triple-negative breast cancer and its association with obesity. Molecular and clinical oncology, 7(6), 935–942. https://doi.org/10.3892/mco.2017.1429
13. Pang, Y., Wei, Y., & Kartsonaki, C. (2022). Associations of adiposity and weight change with recurrence and survival in breast cancer patients: a systematic review and meta-analysis. Breast cancer (Tokyo, Japan), 29(4), 575–588. https://doi.org/10.1007/s12282-022-01355-z
14. Liu, L., Hao, X., Song, Z., Zhi, X., Zhang, S., & Zhang, J. (2021). Correlation between family history and characteristics of breast cancer. *Scientific reports*, *11*(1), 6360. https://doi.org/10.1038/s41598-021-85899-8
15. R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.
16. Surakasula, A., Nagarjunapu, G. C., & Raghavaiah, K. V. (2014). A comparative study of pre- and post-menopausal breast cancer: Risk factors, presentation, characteristics and management. *Journal of research in pharmacy practice*, *3*(1), 12–18. https://doi.org/10.4103/2279-042X.132704

17. Swainson, Michelle G.; Batterham, Alan M.; Tsakirides, Costas; Rutherford, Zoe H.; Hind, Karen; Tauler, Pedro (2017). *Prediction of whole-body fat percentage and visceral adipose tissue mass from five anthropometric variables. PLOS ONE, 12(5), e0177175*–
. doi:10.1371/journal.pone.0177175

Table 1: Distribution of demographic and risk factors by breast cancer subtype

	Luminal (N=2253)	H2E (N=530)	TN (N=1412)
Patient Demographics			
Year of diagnosis			
2004-2006	637 (28.3%)	141 (26.6%)	399 (28.3%)
2007-2008	483 (21.4%)	114 (21.5%)	315 (22.3%)
2009-2011	605 (26.9%)	146 (27.5%)	389 (27.5%)
2012-2015	528 (23.4%)	129 (24.3%)	309 (21.9%)
Age at diagnosis			
<40	326 (14.5%)	59 (11.1%)	207 (14.7%)
40-49	654 (29.0%)	115 (21.7%)	389 (27.5%)
50-59	716 (31.8%)	211 (39.8%)	452 (32.0%)
60-69	557 (24.7%)	145 (27.4%)	364 (25.8%)
Study site			
New Mexico	205 (9.1%)	115 (21.7%)	255 (18.1%)
Seattle	2048 (90.9%)	415 (78.3%)	1157 (81.9%)
Race/ethnicity			
Hispanic	133 (5.9%)	52 (9.8%)	116 (8.2%)
Non-Hispanic White	1832 (81.3%)	408 (77.0%)	1098 (77.8%)
Black	83 (3.7%)	23 (4.3%)	110 (7.8%)
Asian/Pacific Islander	164 (7.3%)	39 (7.4%)	60 (4.2%)
Native American	41 (1.8%)	8 (1.5%)	28 (2.0%)
Stage at diagnosis			
I	1086 (48.2%)	175 (33.0%)	503 (35.6%)
II	858 (38.1%)	224 (42.3%)	661 (46.8%)
III	309 (13.7%)	131 (24.7%)	248 (17.6%)
Menopausal status at diagnosis			
Premenopausal	970 (43.1%)	162 (30.6%)	525 (37.2%)

	Luminal (N=2253)	H2E (N=530)	TN (N=1412)
Perimenopausal	154 (6.8%)	52 (9.8%)	104 (7.4%)
Postmenopausal	1087 (48.2%)	305 (57.5%)	751 (53.2%)
Hysterectomy or period stopped due to other reasons	37 (1.6%)	8 (1.5%)	25 (1.8%)
Missing	5 (0.2%)	3 (0.6%)	7 (0.5%)
Family history of breast cancer			
No	1708 (75.8%)	417 (78.7%)	1069 (75.7%)
Yes	496 (22.0%)	105 (19.8%)	318 (22.5%)
Missing	49 (2.2%)	8 (1.5%)	25 (1.8%)
Insurance status at diagnosis			
Private	1744 (77.4%)	409 (77.2%)	1063 (75.3%)
Uninsured	33 (1.5%)	13 (2.5%)	31 (2.2%)
Medicaid	121 (5.4%)	28 (5.3%)	79 (5.6%)
Medicare/Military/Other public insurance*	122 (5.4%)	33 (6.2%)	87 (6.2%)
Missing	233 (10.3%)	47 (8.9%)	152 (10.8%)
Treatment in the two years after diagnosis			
Hormone therapy use			
No	215 (9.5%)	513 (96.8%)	1390 (98.4%)
Yes	2035 (90.3%)	14 (2.6%)	20 (1.4%)
Missing	3 (0.1%)	3 (0.6%)	2 (0.1%)
Chemotherapy use			
No	1000 (44.4%)	56 (10.6%)	136 (9.6%)
Yes	1249 (55.4%)	472 (89.1%)	1275 (90.3%)
Missing	4 (0.2%)	2 (0.4%)	1 (0.1%)

	Luminal (N=2253)	H2E (N=530)	TN (N=1412)
Surgery & radiation use			
Lumpectomy with radiation	1150 (51.0%)	180 (34.0%)	698 (49.4%)
Total mastectomy	1051 (46.6%)	328 (61.9%)	657 (46.5%)
None of the above/other	52 (2.3%)	22 (4.2%)	57 (4.0%)

*Includes Indian Health Services (IHS)

Table 2: Multivariable cox proportional hazards model of breast cancer recurrence by subtype.

	n (%)	Number of events	Person time at risk (years)	Risk of recurrence	Unadjusted HR	CI	Adjusted HR	CI
Luminal								
<25kg/m^2	781	54	3805.9	0.014	Ref	Ref	Ref	Ref
25-30kg/m^2	521	45	2475.8	0.018	1.21	0.82-1.79	1.15	0.78-1.71
>30kg/m^2	636	57	2989	0.019	1.27	0.87-1.82	1.23	0.84-1.79
H2E								
<25kg/m^2	182	15	663.3	0.023	Ref	Ref	Ref	Ref
25-30kg/m^2	153	18	510.8	0.035	1.55	0.78-3.09	1.42	0.70-2.88
>30kg/m^2	136	26	502.5	0.052	**2.34**	**1.24-4.43**	**2.21**	**1.13-4.32**
TN								
<25kg/m^2	401	92	1264.9	0.073	Ref	Ref	Ref	Ref
25-30kg/m^2	351	62	1146.7	0.054	0.73	0.53-1.01	**0.61**	**0.44-0.85**
>30kg/m^2	441	106	1413.2	0.075	1.02	0.77-1.35	0.89	0.67-1.19

Table 3: Multivariable cox proportional hazards model of breast cancer specific mortality by subtype.

	n (%)	Number of events	Person time at risk (years)	Risk of recurrence	Unadjusted HR	CI	Adjusted HR	CI
Luminal								
<25kg/m^2	788	61	8901	0.007	Ref	Ref	Ref	Ref

25-30kg/m^2	524	46	5810.1	0.008	1.15	0.78-1.68	0.97	0.66-1.43
>30kg/m^2	640	66	6994.5	0.009	1.37	0.96-1.94	1.13	0.79-1.62
H2E								
<25kg/m^2	182	18	1934.2	0.009	Ref	Ref	Ref	Ref
25-30kg/m^2	154	17	1536.6	0.011	1.12	0.58-2.18	1.16	0.58-2.35
>30kg/m^2	137	25	1378	0.018	**1.95**	**1.06-3.58**	**1.95**	**1.01-3.77**
TN								
<25kg/m^2	414	91	3787.2	0.024	Ref	Ref	Ref	Ref
25-30kg/m^2	362	71	3566.1	0.020	0.85	0.62-1.16	**0.72**	**0.52-0.98**
>30kg/m^2	450	111	4030.8	0.028	1.13	0.85-1.49	1.02	0.77-1.35

Table 4: Multivariable cox proportional hazards model of breast cancer recurrence by subtype and menopausal status.

	n (%)	Number of events	Person time at risk (years)	Risk of recurrence	Unadjusted HR	CI	Adjusted HR	CI
Luminal								
<25kg/m^2								
Pre-menopausal	431	38	2082.2	0.018	Ref	Ref	Ref	Ref
Post-menopausal	286	19	1431.5	0.013	Ref	Ref	Ref	Ref
25-30kg/m^2								
Pre-menopausal	218	25	1045.73	0.024	1.33	0.80-2.20	1.20	0.71-2.03
Post-menopausal	263	18	1250.9	0.014	1.11	0.58-2.11	1.11	0.58-2.13
>30kg/m^2								
Pre-menopausal	180	21	814.9	0.026	1.42	0.83-2.42	1.20	0.68-2.11
Post-menopausal	413	32	1967.8	0.016	1.24	0.70-2.18	1.15	0.64-2.06
H2E								
<25kg/m^2								

Pre-menopausal	59	4	198.6	0.02	Ref	Ref	Ref	Ref
Post-menopausal	103	9	377.5	0.024	Ref	Ref	Ref	Ref
25-30kg/m^2								
Pre-menopausal	43	3	160.7	0.019	0.98	0.22-2.40	0.96	0.28-3.35
Post-menopausal	90	13	278.5	0.047	1.91	0.82-4.48	1.61	0.62-4.16
>30kg/m^2								
Pre-menopausal	41	12	136.4	0.088	**4.50**	**1.45-14.0**	**5.03**	**1.95-13.0**
Post-menopausal	84	13	322	0.04	1.71	0.73-4.00	1.50	0.58-3.86
TN								
<25kg/m^2								
Pre-menopausal	172	44	562.4	0.078	Ref	Ref	Ref	Ref
Post-menopausal	196	41	607.7	0.067	Ref	Ref	Ref	Ref
25-30kg/m^2								
Pre-menopausal	128	27	380.8	0.071	0.86	0.53-1.39	0.67	0.41-1.10
Post-menopausal	200	33	678.2	0.049	0.72	0.46-1.14	**0.55**	**0.34-0.88**
>30kg/m^2								
Pre-menopausal	154	38	518.8	0.073	0.92	0.60-1.43	0.85	0.52-1.36
Post-menopausal	246	62	742.6	0.083	1.23	0.82-1.81	0.92	0.61-1.39

Table 5: Multivariable cox proportional hazards model of breast cancer specific mortality by subtype and menopausal status.

	n (%)	Number of events	Person time at risk (years)	Risk of recurrence	Unadjusted HR	CI	Adjusted HR	CI
Luminal								
<25kg/m^2								
Pre-menopausal	434	32	4968.2	0.006	Ref	Ref	Ref	Ref

Post-menopausal	288	23	3210.7	0.007	Ref	Ref	Ref	Ref
25-30kg/m^2								
Pre-menopausal	220	20	2481.8	0.008	1.24	0.71-2.17	0.96	0.53-1.71
Post-menopausal	265	22	2901.3	0.008	1.05	0.59-1.89	1.01	0.55-1.85
>30kg/m^2								
Pre-menopausal	182	19	2039.8	0.009	1.44	0.82-2.53	1.13	0.62-2.04
Post-menopausal	414	42	4474.3	0.009	1.30	0.78-2.17	1.16	0.69-1.96
H2E								
<25kg/m^2								
Pre-menopausal	59	4	627.8	0.006	Ref	Ref	Ref	Ref
Post-menopausal	103	12	1084.3	0.011	Ref	Ref	Ref	Ref
25-30kg/m^2								
Pre-menopausal	43	4	468.8	0.009	1.36	0.34-5.44	0.77	0.14-4.14
Post-menopausal	91	12	853.5	0.014	1.14	0.51-2.54	1.04	0.44-2.49
>30kg/m^2								
Pre-menopausal	41	9	421.8	0.021	3.50	1.08-11.4	4.58	1.03-20.4
Post-menopausal	85	15	831.8	0.018	1.57	0.74-3.36	1.41	0.62-3.26
TN								
<25kg/m^2								
Pre-menopausal	178	41	1726.3	0.024	Ref	Ref	Ref	Ref
Post-menopausal	201	44	1744.1	0.025	Ref	Ref	Ref	Ref
25-30kg/m^2								
Pre-menopausal	130	32	1239.3	0.026	1.05	0.66-1.67	0.80	0.49-1.28
Post-menopausal	207	38	2044.8	0.019	0.78	0.50-1.20	0.65	0.42-1.02
>30kg/m^2								
Pre-menopausal	158	36	1481.4	0.024	0.97	0.62-1.52	0.84	0.52-1.36

Post-menopausal	249	68	2080.3	0.033	1.28	0.88-1.88	1.20	0.81-1.76

Table 6: Multivariable cox proportional hazards model of breast cancer recurrence by subtype and family history.

	n (%)	Number of events	Person time at risk (years)	Risk of recurrence	Unadjusted HR	CI	Adjusted HR	CI
Luminal								
<25kg/m^2								
No family history	619	51	2974.6	0.017	Ref	Ref	Ref	Ref
Any family history*	151	7	769.8	0.009	Ref	Ref	Ref	Ref
25-30kg/m^2								
No family history	389	41	1871.5	0.022	1.30	0.86-1.97	1.21	0.79-1.84
Any family history*	127	3	587.1	0.005	0.58	0.15-2.23	0.47	0.12-1.87
>30kg/m^2								
No family history	479	44	2242.1	0.020	1.16	0.77-1.73	1.09	0.72-1.67
Any family history*	142	11	680.5	0.016	1.84	0.71-4.75	1.96	0.68-5.61
H2E								
<25kg/m^2								
No family history	146	9	560.3	0.016	Ref	Ref	Ref	Ref
Any family history*	34	6	100.3	0.060	Ref	Ref	Ref	Ref
25-30kg/m^2								
No family history	125	13	420.9	0.031	1.90	0.81-4.44	1.96	0.79-4.84
Any family history*	26	4	82.6	0.048	0.70	0.22-2.82	0.54	0.08-3.59
>30kg/m^2								

No family history	101	20	353.5	0.057	3.56	0.81-4.44	**3.50**	**1.53-8.04**
Any family history*	34	6	146.3	0.041	0.70	0.22-2.25	0.69	0.16-3.09
TN								
<25kg/m^2								
No family history	295	66	930.1	0.071	Ref	Ref	Ref	Ref
Any family history*	98	23	320.6	0.072	Ref	Ref	Ref	Ref
25-30kg/m^2								
No family history	276	51	883.7	0.058	0.80	0.55-1.15	0.63	0.43-0.92
Any family history*	74	11	257.7	0.043	0.61	0.30-1.25	0.60	0.29-1.25
>30kg/m^2								
No family history	340	81	1087.6	0.074	1.05	0.76-1.45	0.91	0.65-1.27
Any family history*	95	24	310.4	0.077	1.04	0.59-1.85	0.84	0.45-1.57

* First degree relative defined as a parent, sibling, or child

Table 7: Multivariable cox proportional hazards model of breast cancer specific mortality by subtype and family history.

	n (%)	Number of events	Person time at risk (years)	Risk of recurrence	Unadjusted HR	CI	Adjusted HR	CI
Luminal								
<25kg/m^2								
No family history	707	59	7845.3	0.008	Ref	Ref	Ref	Ref
Any family history*	178	9	2089	0.004	Ref	Ref	Ref	Ref
25-30kg/m^2								

No family history	437	40	4873.2	0.008	1.09	0.73-1.63	0.99	0.64-1.51
Any family history*	142	8	1549.3	0.005	1.15	0.44-2.97	0.72	0.25-2.10
>30kg/m^2								
No family history	517	50	5685	0.009	1.17	0.80-1.70	1.02	0.68-1.54
Any family history*	162	17	1742.3	0.010	2.23	0.99-4.99	1.96	0.76-5.05
H2E								
<25kg/m^2								
No family history	165	12	1787	0.007	Ref	Ref	Ref	Ref
Any family history*	35	8	329.1	0.024	Ref	Ref	Ref	Ref
25-30kg/m^2								
No family history	138	13	1379.8	0.009	1.32	0.60-2.89	1.85	0.74-4.64
Any family history*	29	3	289.2	0.10	0.42	0.11-1.58	0.27	0.05-1.60
>30kg/m^2								
No family history	112	22	1068.8	0.021	**2.97**	**1.47-6.00**	**3.48**	**1.50-8.06**
Any family history*	37	7	403.1	0.017	0.76	0.27-2.09	0.47	0.13-1.62
TN								
<25kg/m^2								
No family history	348	70	3232.9	0.022	Ref	Ref	Ref	Ref
Any family history*	108	20	1046.6	0.019	Ref	Ref	Ref	Ref
25-30kg/m^2								
No family history	315	63	3125.8	0.02	0.96	0.68-1.35	0.76	0.53-1.08
Any family history*	87	12	907.9	0.013	0.70	0.34-1.44	0.66	0.31-1.42

>30kg/m^2								
No family history	384	91	3476.4	0.026	1.20	0.88-1.64	1.03	0.74-1.43
Any family history*	114	28	1069.8	0.026	1.32	0.74-2.34	1.23	0.65-2.33

*First degree relative defined as a parent, sibling, or child