Body Mass Index and Risks of Recurrence and Mortality by Breast Cancer Subtype

Francys C. Verdial Argueta

A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Public Health

University of Washington

2018

Committee:
Christopher I. Li
Sara H. Javid

Program authorized to offer degree:
Epidemiology

University of Washington

Abstract

Body Mass Index and Risks of Recurrence and Mortality by Breast Cancer Subtype

Francys C. Verdial Argueta

Chair of the Supervisory Committee:

Christopher I. Li

Department of Epidemiology

A key modifiable risk factor that may contribute to breast cancer prognosis is body mass index (BMI). Triple negative (TN) and HER2-overexpressing (H2E) breast cancers are particularly aggressive molecular subtypes where lifestyle-focused interventions may be particularly impactful. We conducted a population-based case–case study of 4,557 women aged 20–69 years diagnosed with invasive breast cancer from 2004-2015. Case groups were defined by ER/PR/HER2 status—TN (ER-/PR-/HER2-, n=1,559), H2E (ER-/HER2+, n=615), luminal A (ER+/HER2-, n=2,048), luminal B (ER+/HER2+, n=335). Multivariable-adjusted Cox proportional hazards models were used to evaluate the impact of BMI at diagnosis on recurrence and mortality across each subtype, overall and stratified by menopausal status. Median follow-up was 7-years, with 736 (16%) observed recurrences and 733 (16%) deaths. Among women with TN-tumors, overweight (BMI=25-30kg/m2) women had lower risks of recurrence (HR=0.70, 95%CI=0.52-0.95) and mortality (HR=0.66, 95%CI=0.50-0.88) compared to women with a BMI<25kg/m2. Women with H2E-tumors who were obese (BMI>30kg/m2) had a 2.12-fold (95%CI=1.12-4.04) higher risk of recurrence and 2-fold (95%CI=1.19-3.641) higher risk of mortality than women with BMI<25kg/m2. BMI was not associated with risks of recurrence or mortality among patients with luminal A or luminal B tumors. Previous studies indicate that obese breast cancer survivors have worse outcomes. However,

our results suggest that obesity is associated with increased risks of recurrence and mortality only among younger women with H2E disease. The mechanism underlying these relationships is unclear, but if confirmed, these associations suggest that weight-loss interventions may be particularly beneficial for premenopausal H2E breast cancer patients.

INTRODUCTION

Breast cancer is a heterogeneous disease consisting of distinct molecular subtypes defined by patterns of gene expression or joint tumor marker expression with unique biologic features. Protein expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) is routinely used to classify tumors as: luminal A (ER+ or PR+/HER2-), luminal B (ER+ or PR+/HER2+), HER2-overexpressing (H2E) (ER-/HER2+), and triple negative (TN) (ER-/PR-/HER-2)[1,2]. These different subtypes are clinically meaningful and exhibit distinct clinical profiles, responses to therapy, and oncologic outcomes. While luminal subtypes (ER+) appear to have better prognosis, H2E and TN tumors are associated with worse recurrence rates and survival[3,4].

Though the clinical differences across molecular subtypes have been well-studied, factors influencing recurrence and survival differences are less thoroughly understood. Obesity is an established risk factor for the development of postmenopausal breast cancer[5,6] and has been linked to poor prognosis[7]. Prior studies suggest that the relationship between BMI and breast cancer risk differs by molecular subtype. For instance, obesity has been linked to an increased risk of ER+ cancers among postmenopausal women[8]. In premenopausal women, obesity may be associated with a decreased risk of ER+ breast cancers,[8,9] but contribute to a higher incidence of TN cancers.[9–11] The literature also points to a greater risk of breast-cancer recurrence and mortality with obesity[7,12,13]. Biological differences and the known heterogeneous relationship between obesity and incidence lead us to hypothesize that obesity may have divergent impacts on prognosis among breast cancer subtypes. However, research on recurrence and survival has largely focused on all breast cancer subtypes as one group, limiting our ability to assess the prognostic effect of obesity in specific breast cancer subtypes.

The known differences between molecular subtypes of breast cancer lend biological plausibility to the hypothesis that tumors differing in ER status may respond differently to obesity, contributing to established differences in recurrence and survival. Given that breast cancer remains the most common

cause of cancer and the second leading cause of cancer-related mortality in the United States[14], developing a more comprehensive understanding of how obesity, a modifiable risk factor, may influence breast cancer recurrence and mortality is crucial. TN and H2E breast cancers are particularly aggressive molecular subtypes where lifestyle-focused interventions may be particularly impactful. The aim of the present study is to further our understanding of the impact of obesity on recurrence and survival of different molecular subtypes of breast cancer, particularly TN and H2E breast cancer.

METHODS

Study design and population

We conducted a population-based prospective cohort study of women aged 20–69 years diagnosed with invasive breast cancer from 2004-2015. Potentially eligible participants were identified through the Surveillance, Epidemiology and End Results (SEER) cancer registries serving the Seattle-Puget Sound region and the state of New Mexico. The study was independently approved by Institutional Review Boards at the Fred Hutchinson Cancer Research Center and the University of New Mexico.

Study participants consisted of women 20–69 years old first diagnosed with invasive breast cancer while living in the Seattle-Puget Sound, Washington or Albuquerque, New Mexico greater metropolitan areas between June 1, 2004 and June 30, 2015. Women aged 70 years or older were not included in the study because the incidence of TN and H2E tumors declines sharply after age 70. Wome n with incomplete tumor marker information were not eligible for the study. Breast cancer subgroups were defined by joint ER/PR/HER2 status, including TN (ER-/PR-/HER2-), luminal A (ER+/HER2+), and luminal B (ER+/HER2+). All incident TN and H2E breast cases were enrolled in the study, but only a

randomly selected sample of ER+ (luminal A and B) cases was selected (matched by age, year of diagnosis, and study site).

In New Mexico, the medical records of all 681 eligible breast cancer cases (response rate: 100%) were reviewed under an IRB approved waiver of consent. In Seattle, 2,882 of 4,508 (response rate: 64%) eligible women newly diagnosed with invasive breast cancer during the study period were enrolled in addition to 994 eligible participants identified from prior studies with overlapping eligibility criteria (the design and methods of these studies have been previously described[15,16]). Seattle participants were further approached for their consent to participate in a structured interview covering a variety of topics related to breast cancer risk factors. Among 3,876 enrolled participants, interview and medical records data were both obtained for 2,965, medical record only data were available for 536 and interview only data were available for 375 women. To overcome the potential bias that would have resulted from only including participants who were alive at enrollment, eligible deceased women were enrolled at both study sites through a waiver of consent. Data on deceased women were obtained only through the review of medical records. For this analysis, we excluded 40 women for which BMI data was not available. Our final cohort included a total of 4,517 women with breast cancer, 2,036 luminal A, 333 luminal B, 1,539 TN, and 609 H2E cases.

Data collection

Data on demographic and clinical factors were collected via medical record abstraction for participants at the New Mexico site and via both medical record review and structured telephone interview for participants in Seattle. For all variables, the primary source of data was medical records. Interview data were used to supplement data missing from medical records.

Body mass index (BMI) at the time of diagnosis was the primary exposure evaluated. This was obtained through review of medical records from inpatient visits, oncology visits, and primary care visits

recording patient's height and weight. Interview data was used when medical record data was not available. Additionally, we collected information on other risk factors for recurrence and mortality, including reproductive history, use of oral contraceptives (OCs), and menopausal hormone therapy (HT) over the five years prior to breast cancer diagnosis, family history of breast cancer, and menopausal status. Breast cancer-specific information, such as stage, grade, and hormone receptor status, was collected from pathology, surgery, and laboratory reports. We ascertained recurrence from the medical record and death through linkage with death certificate data. To ensure consistency in data abstraction and coding between sites, a random 10% of abstracted records were selected for exchange and review between study sites.

Analyses

We categorized BMI (kg/m^2) at time of diagnosis based on criteria defined by the World Health Organization, where normal BMI is <25 kg/m2, overweight is 25.0–29.9 kg/m2, and obese is ≥30 kg/m2. The primary outcomes assessed were recurrence-free survival and breast cancer-specific survival. Recurrence-free survival (RFS) was defined as time from diagnosis to local or distant recurrence or death from any cause, whichever occurred first. Breast cancer-specific survival (BCSS) was defined as time from diagnosis to death due to breast cancer. Death due to breast cancer was defined as death occurring after recurrence of breast cancer. Follow-up time was calculated from the date of diagnosis to the date of death or recurrence, last known follow-up, or date of study truncation. Patients were censored at last follow-up if the event did not occur.

The demographic and clinical characteristics of patients with different breast cancer subtypes were examined using the $\chi 2$ test and ANOVA test for categorical and continuous variables, respectively. We used multivariable-adjusted Cox proportional hazards models to evaluate the impact of BMI at diagnosis on RFS and BCSS across each subtype, reporting hazard ratios and 95% confidence intervals

(CI). We excluded 338 patients with stage IV disease or missing stage data from the recurrence analysis. All models were adjusted for age at diagnosis (5-year categories), race, stage, receipt of surgery (yes/no), receipt of chemotherapy (yes/no), receipt of radiation therapy (yes/no), receipt of hormonal treatment for luminal and H2E subtypes (yes/no), and receipt of Herceptin (yes/no) for H2E subtype. Additional analyses stratified by menopausal status were conducted, excluding 7 women with unknown menopausal status, and menopausal status was evaluated as a potential effect modifier. Menopausal status was determined from medical records. Postmenopausal women included those who had natural menopause or induced menopause by bilateral oophorectomy and 338 Perimenopausal cases were included in the premenopausal group. Analyses were performed using Stata/SE (Stata Corp, College Station, TX).

RESULTS

Demographic and clinical characteristics by breast cancer subtype are summarized in Table 1. Women with luminal A tumors were more likely to be non-Hispanic white, current estrogen + progestin HT users and OC users, and to present at earlier stage as compared to women with other breast cancer subtypes. Women with luminal B cancers were younger, more frequently premenopausal, nulliparous, never users of HT, and current users of OC compared to women with other subtypes. Women with TN disease were more likely to be African American and to have used OCs. Women with H2E subtypes were somewhat more likely to be postmenopausal and have higher stage disease. With regards to BMI, women with luminal B tumors were more likely to have a BMI <25 kg/m^2 while women with TN tumors were most likely to be obese.

Median follow-up was 7-years. At the time of this analysis, 571 (15%) women had experienced a recurrence and 709 (16%) of all women had died. Of all deaths, 465 (10% of total) occurred after cancer

recurrence and were attributed to breast cancer. Table 2 summarizes the multivariable Cox proportional hazards models for the two primary end points (RFS and BCSS) adjusted for age at diagnosis, race, stage, and treatment. Among women with TN-tumors, overweight (BMI=25-30kg/m^2) women had lower risks of recurrence and mortality (HR 0.62 95% CI 0.45-0.85) compared to women with a BMI<25kg/m^2. Women with H2E-tumors who were obese (BMI>30kg/m2) had a 2.12-fold (95%CI=1.12-4.04) higher risk of recurrence and 2.08-fold (95%CI 1.19-3.64) higher risk of mortality than those with BMI<25kg/m^2. BMI was not associated with risks of recurrence or mortality among patients with luminal A or luminal B tumors. Menopausal status was not found to be a significant effect modifier of the association between BMI and recurrence or survival. Thus, stratified results are not presented.

DISCUSSION

Data from this large population-based study suggests that there is heterogeneity in the relationship between BMI and prognosis of breast cancer by molecular subtype. While previous studies indicate that obese breast cancer survivors have worse outcomes, our results suggest that obesity may contribute to an increased risks of recurrence and mortality only among women with H2E disease but not to risks of recurrence and mortality of either luminal or TN breast cancer.

Many studies have linked obesity to prognosis among women with breast cancer. In a cohort of 18,967 women treated for early-stage breast cancer in Denmark, obesity was found to be an independent prognostic factor for developing distant metastatic disease and death due to breast cancer. When data were adjusted for disease characteristics, a BMI of 30 kg/m^2 or more[17] was significantly linked to a 46% increase in risk of distant metastatic recurrence at 10 years and a 38% increased risk of dying from breast cancer at 30 years. In a pooled analysis of 43 studies of women treated for breast cancer between 1963 and 2005, obese women had a 33% increased risk of both breast cancer-specific and overall mortality. [7] Both reports were limited in their ability to evaluate this relationship by

molecular subtype. Studies looking at prognostic impact of obesity on tumors with different ER status suggest the negative effect of obesity occurs predominantly among patients with ER+ disease. Sparano and colleages[18] examined recurrence and survival in three populations from adjuvant trials from the Eastern Cooperative Oncology group. They found obesity to be associated with inferior outcomes only in the cohort with ER+ breast cancer. Recent studies focused on women with TNBC have not found a relation between obesity and prognosis[19–22]. Few studies have included a group of women with H2E disease[23–25] and, to a best of our knowledge, no study has reported an association between obesity and breast cancer prognosis specific to this subgroup. Consistent with these studies, our data supports a heterogeneous relationship between obesity and breast cancer prognosis by receptor subtype. However, we found obesity to be linked to inferior outcomes only among the subset of patients with H2E disease and, conversely, that being overweight is linked to improved outcomes among with TN disease.

Several mechanisms have been postulated to explain the adverse effects of obesity on breast cancer incidence, recurrence, and survival. Increased production of estrogen in excess adipose tissue leading to increased estrogen levels, particularly among postmenopausal women, may contribute to this relationship. The relationship linking menopausal status and BMI with prognostic outcome among women with breast cancer is complex; however, there is a growing body of evidence suggesting that, contrary to the relationship seen in breast cancer incidence, the relationship between obesity and prognosis is independent of menopausal status[26]. This is supported by our study. Non-hormonal pathways, such as obesity-related increased levels of insulin, insulin like growth factors, and proinflammatory mediators promoting tumor growth, are also though to contribute to this relationship. It remains uncertain which specific factors may drive prognosis of particular breast cancer subtypes.

In considering the results of this study, it is important to recognize its limitations. First, we do not have data on several important factors, such as diet, physical activity, and BMI after diagnosis that may be correlated with both exposure and outcomes and could potentially affect their relationship. Second, recall bias is a potential concern for most retrospective studies, but in this study BMI was obtained from medical records for the majority of participants. There is also the potential for misclassification bias. ER, PR, and HER2 information was abstracted from cancer registries, which gather information from various sources with likely variable practices. Nonetheless, any misclassification is likely non-differential and not related to the exposure of interest. Lastly, with respect to generalizability, our population was predominantly non-Hispanic. We included few African American women but did recruit a substantially larger number of Hispanic women than have been included in prior similar studies.

This study contributes to the evidence that the effect of obesity differs across the major breast cancer subtypes and adds to our understanding of the prognosis of clinically aggressive TN and H2E subtypes. This data spawns new questions as to the mechanism(s) underlying worse breast ca outcomes among obese H2E patients, which could include inadequate dosing of chemo and/or targeted biologic therapies (trastuzumab, pertuzumab)

REFERENCES

1. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406(6797):747-752. doi:10.1038/35021093.
2. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc Natl Acad Sci U S A*. 2003;100(14):8418-8423. doi:10.1073/pnas.0932692100.
3. Dawood S, Hu R, Homes MD, et al. Defining breast cancer prognosis based on molecular phenotypes: results from a large cohort study. *Breast Cancer Res Treat*. 2011;126(1):185-192. doi:10.1007/s10549-010-1113-7.
4. Onitilo AA, Engel JM, Greenlee RT, Mukesh BN. Breast Cancer Subtypes Based on ER/PR and Her2 Expression: Comparison of Clinicopathologic Features and Survival. *Clin Med Res*. 2009;7(1-2):4-13. doi:10.3121/cmr.2009.825.
5. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol*. 2000;152(6):514-527. http://www.ncbi.nlm.nih.gov/pubmed/10997541. Accessed May 14, 2018.
6. Trentham-Dietz A, Newcomb PA, Storer BE, et al. Body Size and Risk of Breast Cancer. *Am J Epidemiol*. 1997;145(11):1011-1019. doi:10.1093/oxfordjournals.aje.a009057.
7. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. *Breast Cancer Res Treat*. 2010;123(3):627-635. doi:10.1007/s10549-010-0990-0.
8. Munsell MF, Sprague BL, Berry DA, Chisholm G, Trentham-Dietz A. Body Mass Index and Breast Cancer Risk According to Postmenopausal Estrogen-Progestin Use and Hormone Receptor Status. *Epidemiol Rev*. 2014;36(1):114-136. doi:10.1093/epirev/mxt010.
9. Chen L, Cook LS, Tang M-TC, et al. Body mass index and risk of luminal, HER2-overexpressing, and

triple negative breast cancer. *Breast Cancer Res Treat*. 2016;157(3):545-554. doi:10.1007/s10549-016-3825-9.

10. Gaudet MM, Press MF, Haile RW, et al. Risk factors by molecular subtypes of breast cancer across a population-based study of women 56 years or younger. *Breast Cancer Res Treat*. 2011;130(2):587-597. doi:10.1007/s10549-011-1616-x.
11. Kwan ML, Kushi LH, Weltzien E, et al. Epidemiology of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. *Breast Cancer Res*. 2009;11(3):R31. doi:10.1186/bcr2261.
12. Jiralerspong S, Kim ES, Dong W, Feng L, Hortobagyi GN, Giordano SH. Obesity, diabetes, and survival outcomes in a large cohort of early-stage breast cancer patients. *Ann Oncol*. 2013;24(10):2506-2514. doi:10.1093/annonc/mdt224.
13. Azrad M, Demark-Wahnefried W. The association between adiposity and breast cancer recurrence and survival: A review of the recent literature. *Curr Nutr Rep*. 2014;3(1):9-15. doi:10.1007/s13668-013-0068-9.
14. U.S. Cancer Statistics Working Group. *United States Cancer Statistics: 1999-2014 Incidence and Mortality Web-Based Report*. Atlanta; 2017. https://nccd.cdc.gov/uscs/. Accessed October 20, 2017.
15. Li CI, Malone KE, Porter PL, et al. Relationship between Menopausal Hormone Therapy and Risk of Ductal, Lobular, and Ductal-Lobular Breast Carcinomas. *Cancer Epidemiol Biomarkers Prev*. 2008;17(1):43-50. doi:10.1158/1055-9965.EPI-07-0558.
16. Li CI, Beaber EF, Tang MTC, Porter PL, Daling JR, Malone KE. Effect of depo-medroxyprogesterone acetate on breast cancer risk among women 20 to 44 years of age. *Cancer Res*. 2012;72(8):2028-2035. doi:10.1158/0008-5472.CAN-11-4064.
17. Ewertz M, Jensen M-B, Gunnarsdóttir KÁ, et al. Effect of obesity on prognosis after early-stage

breast cancer. *J Clin Oncol*. 2011;29(1):25-31. doi:10.1200/JCO.2010.29.7614.

18. Jain R, Strickler HD, Fine E, Sparano JA. Clinical Studies Examining the Impact of Obesity on Breast Cancer Risk and Prognosis. *J Mammary Gland Biol Neoplasia*. 2013;18(3-4):257-266. doi:10.1007/s10911-013-9307-3.

19. Mowad R, Chu QD, Li BDL, Burton G V., Ampil FL, Kim RH. Does obesity have an effect on outcomes in triple-negative breast cancer? *J Surg Res*. 2013;184(1):253-259. doi:10.1016/j.jss.2013.05.037.

20. Dawood S, Lei X, Litton JK, Buchholz TA, Hortobagyi GN, Gonzalez-Angulo AM. Impact of Body Mass Index on Survival Outcome Among Women With Early Stage Triple-Negative Breast Cancer. *Clin Breast Cancer*. 2012;12(5):364-372. doi:10.1016/j.clbc.2012.07.013.

21. Tait S, Pacheco JM, Gao F, Bumb C, Ellis MJ, Ma CX. Body mass index, diabetes, and triple-negative breast cancer prognosis. *Breast Cancer Res Treat*. 2014;146(1):189-197. doi:10.1007/s10549-014-3002-y.

22. Ademuyiwa FO, Groman A, O'Connor T, Ambrosone C, Watroba N, Edge SB. Impact of body mass index on clinical outcomes in triple-negative breast cancer. *Cancer*. 2011;117(18):4132-4140. doi:10.1002/cncr.26019.

23. Widschwendter P, Friedl TW, Schwentner L, et al. The influence of obesity on survival in early, high-risk breast cancer: results from the randomized SUCCESS A trial. *Breast Cancer Res*. 2015;17(1):129. doi:10.1186/s13058-015-0639-3.

24. Cho WK, Choi DH, Park W, et al. Effect of Body Mass Index on Survival in Breast Cancer Patients According to Subtype, Metabolic Syndrome, and Treatment. *Clin Breast Cancer*. April 2018. doi:10.1016/J.CLBC.2018.04.010.

25. Sparano JA, Wang M, Zhao F, et al. Obesity at diagnosis is associated with inferior outcomes in hormone receptor-positive operable breast cancer. *Cancer*. 2012;118(23):5937-5946.

doi:10.1002/cncr.27527.

26. Holmberg lars, Lund E, Bergström R, Adami HO, Meirik O. Oral contraceptives and prognosis in breast cancer: effects of duration, latency, recency, age at first use and relation to parity and body mass index in young women with breast cancer. *Eur J Cancer*. 1994;30A(3):351-354. https://www.ejcancer.com/article/0959-8049(94)90255-0/pdf. Accessed June 4, 2018.

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

	Luminal A		Luminal B		Triple negative		H2E	
	n=1,854	%	n=305	%	n=1,423	%	n=572	%
Year of diagnosis								
2004-2006	583	29%	80	24%	426	28%	158	26%
2007-2009	614	30%	118	35%	500	32%	182	30%
2010-2012	518	25%	84	25%	393	26%	171	28%
2013-2015	321	16%	51	15%	220	14%	98	16%
Study Site								
Seattle	1850	91%	292	88%	1238	80%	469	77%
New Mexico	186	9%	41	12%	301	20%	140	23%
Age at diagnosis (years)								
<40	271	13%	78	23%	221	14%	72	12%
40-49	571	28%	121	36%	430	28%	139	23%
50-59	655	32%	89	27%	492	32%	233	38%
60-69	539	26%	45	14%	396	26%	165	27%
Race/ethnicity								
Non-Hispanic white	1660	82%	254	76%	1178	77%	468	77%
Hispanic white	119	6%	29	9%	136	9%	61	10%
African American	72	4%	15	5%	127	8%	28	5%
Asian/Pacific Islander	150	7%	26	8%	65	4%	41	7%
Native American	35	2%	9	3%	33	2%	11	2%
First-degree family history of breast cancer								
Yes	453	22%	56	17%	350	23%	116	19%
No	1528	75%	269	81%	1154	75%	477	78%
Missing	55	3%	8	2%	35	2%	17	3%
BMI (kg/m^2)								
<25	813	40%	151	45%	516	34%	235	39%
25-29.9	561	28%	93	28%	460	30%	193	32%
≥30	662	33%	89	27%	563	37%	181	30%
Menopausal Status								
Premenopausal	842	41%	185	56%	573	37%	197	32%
Perimenopausal	143	7%	21	6%	116	8%	58	10%
Postmenopausal	1050	52%	126	38%	847	55%	352	58%

Unknown/Missing	1	0%	1	0%	3	0%	2	0%
Number of full-term pregnancies								
0	500	25%	82	25%	342	22%	123	20%
1	336	17%	69	21%	286	19%	103	17%
2	768	38%	107	32%	523	34%	225	37%
≥3	430	21%	75	23%	387	25%	155	25%
Missing	2	0%	0	0%	1	0%	3	0%
Age at fist full-term pregnancy (years) **								
<20	218	14%	37	15%	213	18%	75	16%
20-24	410	27%	67	27%	363	30%	142	29%
25-29	421	27%	69	27%	288	24%	108	22%
≥30	433	28%	70	28%	247	21%	114	24%
Missing	52	3%	8	3%	85	7%	44	9%
Breast feeding history								
Yes	1053	52%	173	52%	543	35%	247	41%
No	230	11%	33	10%	182	12%	70	11%
Missing	753	37%	127	38%	814	53%	292	48%
Smoking status at time of diagnosis								
Never	1162	57%	192	58%	850	55%	347	57%
Current	240	12%	44	13%	220	14%	89	15%
Former	549	27%	83	25%	411	27%	150	25%
Not current, NOS	81	4%	12	4%	53	3%	22	4%
Missing	4	0%	2	1%	5	0%	1	0%
Menopausal hormone use at diagnosis								
Never (w/in 5y)	1668	82%	298	89%	1227	80%	492	81%
Former	108	5%	11	3%	99	6%	42	7%
Current estrogen only	97	5%	12	4%	90	6%	29	5%
Current estrogen + progestin	112	6%	6	2%	32	2%	10	2%
Missing	51	3%	6	2%	91	6%	36	6%
Hormonal OC use at diagnosis								
Never (w/in 5y)	1635	80%	257	77%	1090	71%	476	78%
Former	108	5%	27	8%	92	6%	26	4%

Current	207	10%	35	11%	103	7%	29	5%
Ever with unknown end date	44	2%	5	2%	62	4%	11	2%
Missing	42	2%	9	3%	76	5%	30	5%
TNM stage		0%						
I	980	48%	105	32%	502	33%	176	29%
II	725	36%	132	40%	659	43%	223	37%
III	246	12%	60	18%	240	16%	131	22%
IV	63	3%	31	9%	76	5%	62	10%
Missing	22	1%	5	2%	62	4%	17	3%
Surgical treatment		0%						
No surgery	60	3%	12	4%	65	4%	35	6%
Breast-conservation	969	48%	124	37%	718	47%	200	33%
Mastectomy	818	40%	165	50%	630	41%	332	55%
Missing	189	9%	32	10%	126	8%	42	7%
Chemotherapy		0%						
Yes	940	46%	265	80%	1271	83%	505	83%
No	903	44%	37	11%	142	9%	63	10%
Missing	193	9%	31	9%	126	8%	41	7%
Radiation		0%						
Yes	1278	63%	213	64%	978	64%	347	57%
No	559	27%	88	26%	429	28%	217	36%
Missing	199	10%	32	10%	132	9%	45	7%
Endocrine therapy		0%						
Yes	1663	82%	270	81%	21	1%	13	2%
No	178	9%	33	10%	1390	90%	553	91%
Missing	195	10%	30	9%	128	8%	43	7%

OC: oral contraceptive

* Among post-menopausal women

** Among 3,464 parous women

Table 2. Multivariable Cox Proportional Hazards Model of Breast Cancer Recurrence and Survival by Breast Cancer Subtype.

Breast Cancer Recurrence	**Luminal A**		**Luminal B**		**Triple negative**		**H2E**	
	n= 1,748 Time at risk= 8,313 years Number of events= 184		n= 268 Time at risk= 1,226 years Number of events= 32		n= 1,267 Time at risk= 4,046 years Number of events= 282		n= 487 Time at risk= 1,731 years Number of events= 67	
BMI (m/kg^2)†	**Hazard ratio[a]**	**95% CI**	**Hazard ratio[a]**	**95% CI**	**Hazard ratio[b]**	**95% CI**	**Hazard ratio[c]**	**95% CI**
< 25	ref		ref		ref		ref	
25-30	1.21	0.84-1.75	1.35	0.54-3.39	0.62*	0.45-0.85	1.45	0.75-2.83
>30	1.08	0.76-1.55	1.25	0.51-3.05	0.93	0.70-1.23	2.12*	1.12-4.04
Breast Cancer-Specific Survival	**Luminal A**		**Luminal B**		**Triple negative**		**H2E**	
	n= 1,809 Time at risk= 11,986 years Number of events= 127		n= 295 Time at risk= 1,899 years Number of events= 21		n= 1,344 Time at risk= 7,503 years Number of events= 241		n= 543 Time at risk= 3,158 years Number of events= 56	
BMI (m/kg^2)†	**Hazard ratio[a]**	**95% CI**	**Hazard ratio[a]**	**95% CI**	**Hazard ratio[a]**	**95% CI**	**Hazard ratio[a]**	**95% CI**
< 25	ref		ref		ref		ref	
25-30	0.95	0.64-1.40	1.29	0.47-3.50	0.66*	0.50-0.88	0.93	0.49-1.75
>30	1.20	0.85-1.69	1.18	0.47-3.01	0.89	0.67-1.17	2.08*	1.19-3.64

Body mass index (BMI); Her2-overexpressing (H2E). †BMI: median 26.9 (IQR 8.5). [a]Adjusted for age, race, stage, surgery type, chemotherapy, radiation, endocrine therapy. [b]Adjusted for age, race, stage, surgery type, chemotherapy, radiation. [c]Adjusted for age, race, stage, surgery type, chemotherapy, radiation, endocrine therapy, targeted therapy with Herceptin. *p-value<0.05.