Obesity and Breast Cancer Metastasis across Genomic Subtypes

Linnea T. Olsson[1], Andrea Walens[2], Alina M. Hamilton[3], Halei C. Benefield[1], Jodie M. Fleming[2,4], Lisa A. Carey[2], Stephen D. Hursting[5], Kevin P. Williams[6], and Melissa A. Troester[1,2,3]

ABSTRACT

Background: Obese women have higher risk of aggressive breast tumors and distant metastasis. However, obesity has rarely been assessed in association with metastasis in diverse populations.

Methods: In the Carolina Breast Cancer Study Phase 3 (2008–2013), waist-to-hip ratio (WHR), body mass index (BMI), and molecular subtype [PAM50 risk-of-recurrence (ROR) score] were assessed. Obesity measures were evaluated in association with metastasis within five years of diagnosis, overall and stratified by race and ROR score. Absolute risk of metastasis and risk differences between strata were calculated using the Kaplan–Meier estimator, adjusted for age, grade, stage, race, and ER status. Relative frequency of metastatic site and multiplicity were estimated in association with obesity using generalized linear models.

Results: High-WHR was associated with higher risk of metastasis (5-year risk difference, RD, 4.3%; 95% confidence interval, 2.2–6.5). It was also associated with multiple metastases and metastases at all sites except brain. The 5-year risk of metastasis differed by race (11.2% and 6.9% in Black and non-Black, respectively) and ROR score (19.5% vs. 6.6% in high vs. low-to-intermediate ROR-PT). Non-Black women and those with low-to-intermediate ROR scores had similar risk in high- and low-WHR strata. However, among Black women and those with high ROR, risk of metastasis was elevated among high-WHR ($RD_{Black/non\text{-}Black} = 4.6\%$, $RD_{High/Low\text{-}Int} = 3.1\%$). Patterns of metastasis were similar by BMI.

Conclusions: WHR is associated with metastatic risk, particularly among Black women and those with high-risk tumors.

Impact: Understanding how risk factors for metastasis interact may help in tailoring care plans and surveillance among patients with breast cancer.

Introduction

Obesity is an informative patient-level prognostic factor for women with breast cancer. Previous studies have demonstrated associations between adiposity or obesity and increased risk of aggressive tumors (1–3) and mortality (1, 4–11). However, few previous studies have examined the association between obesity and metastasis, overall or according to other prognostic factors such as genomic risk score. Metastatic disease is an important endpoint because it causes the majority of breast cancer–related mortality and because women with metastatic breast cancer often receive additional therapy, report a higher burden of disease- or treatment-related symptoms (12, 13), and experience decreased physical and emotional health-related quality of life (12–15). Identifying women at highest risk for metastasis has been based largely on clinicopathological variables, such as grade, stage, and hormone receptor status, but genomic assays such as Oncotype DX and Prosigna have increasingly become standard of care (16–19). Although obesity is associated with elevated risk for high genomic risk tumors (20), the relationship between obesity and metastasis among those with high genomic risk or other markers of aggressive tumor subtype is not well understood.

We investigated the relationship between breast cancer metastasis and obesity, defined by waist-to-hip ratio (WHR) greater than 0.85 and body mass index (BMI) of 30 or greater. We emphasize the WHR results because although BMI is a commonly reported metric, it does not measure central adiposity, which has previously been shown to have stronger relationships with subtype-specific breast cancer risk in Black women (21–23). Furthermore, Black women tend to have more lean mass and less fat mass or visceral adipose tissue than White women (24, 25), thus it is important to assess a range of anthropometry measures in diverse populations. We hypothesized that the relationship between WHR-defined obesity and 5-year risk of distant metastasis depends upon race and genomic risk scores. We evaluated this question using data from the third phase of the Carolina Breast Cancer Study (CBCS3). This study was designed to investigate the unique experiences of Black women with breast cancer, so we here compare risk of metastasis among Black women to that of non-Black women, the majority of whom reported their race as White.

Materials and Methods

Study population

CBCS3 is a prospective, population-based cohort of women with incident breast cancer recruited from 44 counties in North Carolina between 2008 and 2013. Cases were identified using rapid case ascertainment aided by the North Carolina Central Cancer Registry. Eligible women were between 20 and 74 years old with a first primary breast cancer. Black and young (20–49 years old) women were oversampled to investigate race- and age-related disparities. We view race as a social construct that includes exposure to a variety of stressors,

[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. [2]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. [3]Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. [4]Department of Biological and Biomedical Sciences, North Carolina Central University, Durham, North Carolina. [5]Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. [6]Biomanufacturing Research Institute and Technology Enterprise, North Carolina Central University, Durham, North Carolina.

K.P. Williams and M.A. Troester contributed as co-senior authors of this article.

Corresponding Author: Melissa A. Troester, University of North Carolina at Chapel Hill, 253 Rosenau Hall, 135 Dauer Drive, Chapel Hill, NC 27599. Phone: 919-966-7408; E-mail: troester@unc.edu

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social determinants of health, and structural racism. We adopt a cells-to-society framework where multiple levels from molecular to tissue to individual and community-level factors are integrated to alter risk (26). The majority of non-Black ($n = 1{,}410$) participants in the Carolina Breast Cancer Study Phase 3 self-identified as White ($n = 1{,}332$), with a small proportion identifying as American Indian/Alaska Native ($n = 12$), Asian/Pacific Islander ($n = 30$), or "other" ($n = 36$). The study was approved by the University of North Carolina Institutional Review Board in accordance with revised U.S. Common rule. Study participants provided written informed consent before study entry.

For the present analysis, participants with *de novo* metastases (stage IV at diagnosis, $n = 109$) were excluded, as were participants missing data on adjustment variables, including grade and stage ($n = 122$). The final population included 2,767 eligible women with stage I–III breast cancer at diagnosis. Of these women, 1,321 had molecular assay data from which ROR-PT scores were calculated at the time of analysis. Follow-up for the study began at diagnosis and women were followed until they developed an incident metastasis, accrued five years of follow-up after diagnosis, or were lost to follow-up (LTF). Of the 2,797 women included in the study, 278 (∼10%) were LTF before five years of follow-up had accrued or an outcome had occurred. The mean follow-up time for those LTF was 3.1 years.

Data collection

Metastasis was defined as any incident distant recurrence between diagnosis date and five years after diagnosis ($n = 239$). Data were truncated at five years because all participants in the CBCS3 had five years of follow-up. Cancer recurrence was medically confirmed following initial self-report by patients at annual follow-up contact conducted over the phone by trained interviewers. Study abstractors confirmed recurrence by reviewing diagnostic biopsies, surgical pathology reports, and radiographic imaging reports for recurrent tumors. Recurrences were only recorded for patients who were considered cancer free as determined from their electronic health records. Site of distant recurrence and multiplicity of recurrences, when applicable, were abstracted from medical records. Site of metastasis was categorized either as a five-level categorical variable (bone, brain, liver, lung/pleura, other) or as a binary variable (single vs. multiple). The "other" category included distant lymph node, skin, peritoneal, and other metastases. Up to three sites identified at metastatic diagnosis were reported.

In-person interviews were conducted by trained nurses, who measured waist and hip circumference and collected data on sociodemographic factors and healthcare access via a baseline questionnaire. For the current study, obesity was defined as a WHR greater than a cutoff point of 0.85 or BMI of 30 or greater, selected on the basis of the current recommendations from the World Health Organization (27). In our study population, there was approximately 63% agreement between BMI- and WHR-defined obesity status. Data on clinical characteristics (stage, grade, clinical measurement of IHC status of ER) were abstracted from medical records and pathology reports.

Gene expression analysis

Formalin-fixed, paraffin-embedded tissues were obtained and reviewed for a subset of cases as has been reported previously (28). Briefly, RNA was isolated using RNeasy FFPE Kits (Qiagen) and Nanostring gene expression assays were performed at UNC. Gene expression data were cleaned and normalized as described previously (29). The PAM50 predictor, a research-only version of a clinical 50-gene assay, was used to calculate the risk-of-recurrence (ROR) score, in this case emphasizing ROR-PT, which incorporates the gene expression data on tumor subtype, along with proliferation score (P) and tumor size (T; ref. 30). The ROR-PT score parallels clinical versions of the test in classifying tumors as low-, intermediate-, or high-risk based on these characteristics (30).

Statistical analyses

Five-year cumulative incidence of metastasis was estimated using the Kaplan–Meier (KM) estimator and risk differences were calculated comparing women with high WHR to those with low WHR. Overall and genomic risk score-stratified KM models were adjusted with inverse probability weights (IPW) conditional on grade, stage, age, race, and ER status, and 95% confidence intervals were calculated by nonparametric bootstrap. In race-stratified models, IPW was conditional on grade, stage, age, and ER status only. Grade and stage were modeled as categorical variables with three levels, age was modeled using a restricted cubic spline, ER status categorized as positive or negative from clinical records, and race was classified as Black or non-Black, based on self-report. Of the 1,410 non-Black women included in the study, 94.5% reported their race as White. Again, we include race here as a social construct, representing many social and environmental factors.

To describe the difference in site-specific metastasis by WHR, generalized linear models specified with binomial family and identity link were used to calculate unadjusted relative frequency differences (RFD) and 95% confidence intervals. RFDs may be interpreted as the difference in relative frequency (prevalence) between the index and referent groups. Participants ($n = 112$) with multiple metastasis were included in all relevant site-specific models. All statistical analyses were conducted using R version 3.6.

Data availability

The data analyzed in this study are available from the Carolina Breast Cancer Study (https://unclineberger.org/cbcs/). Restrictions apply to the availability of these data, which were used under data agreements for this study. Data are not publicly available; however, investigators may submit a letter of intent to gain access upon reasonable request.

Results

Participant and tumor characteristics can be found in **Table 1**. WHR appeared to be roughly normally distributed, ranging from 0.57 to 1.35 with both a mean and median of 0.85. The median WHR for Black and non-Black women were 0.87 and 0.84, respectively. Approximately 57.5% of Black and 42.4% of non-Black women were categorized as high-WHR based on the 0.85 WHR cutoff point. Median BMI measurements for Black and non-Black women were 32.0 and 27.4, respectively. Using a cutoff point of 30 for classification of obesity, 61.9% of Black women and 34.3% of non-Black women were classified as obese. The distributions of WHR and BMI both were right-shifted for Black participants, but the distribution of WHR was more similar between Black and non-Black participants (see Supplementary Fig. S1). Approximately 48% of the overall study population was classified as high-WHR, consistent with the high prevalence of overweight and obesity among women in the state of North Carolina (31). High-WHR women were slightly older, had slightly more advanced or aggressive (stage II/III, ER-negative, and grade 3) disease, and a larger proportion were Black. The distributions of IHC-based subtype were similar between high-WHR and low-WHR women. Women with obese BMI (≥30) displayed similar distributions of clinical characteristics as women with high-WHR.

Table 1. Demographic and clinical characteristics of study participants by WHR-defined obesity status.

	Overall Mean (SD) or *n* (%)	Low WHR Mean (SD) or *n* (%)	High WHR Mean (SD) or *n* (%)
n	2,767	1,434 (51.8)	1,333 (48.2)
Age	51.7 (11.1)	50.2 (11.2)	53.4 (10.9)
WHR	0.85 (0.08)	0.79 (0.04)	0.91 (0.05)
BMI (continuous)	30.6 (7.5)	28.6 (7.1)	32.8 (7.2)
BMI categories			
Normal	679 (24.6)	518 (36.2)	161 (12.1)
Overweight	763 (27.6)	412 (28.8)	351 (26.3)
Obese	1,323 (47.8)	502 (35.1)	821 (61.6)
Missing	2	2	0
ROR-PT			
Low–intermediate	1,015 (76.8)	532 (77.4)	483 (76.2)
High	306 (23.2)	155 (22.6)	151 (23.8)
Race			
Non-Black	1,410 (51.0)	844 (58.9)	566 (42.4)
Black	1,357 (49.0)	590 (41.1)	767 (57.5)
Grade			
1	570 (20.6)	302 (21.1)	268 (20.1)
2	1,054 (38.1)	561 (39.1)	493 (37.0)
3	1,143 (41.3)	571 (39.8)	572 (42.9)
Stage			
I	1,174 (42.4)	635 (44.3)	539 (40.4)
II	1,174 (42.4)	594 (41.4)	580 (43.5)
III	419 (15.1)	205 (14.3)	214 (16.1)
ER Status			
Negative	729 (36.4)	356 (24.8)	373 (28.0)
Positive	2,037 (63.6)	1,077 (75.2)	960 (72.0)
Missing	1	1	0

Differences in incidence of metastasis

We evaluated incidence of metastasis among high-WHR and low-WHR participants, both overall and stratified by race and ROR scores (**Table 2**). Women with high WHR experienced higher 5-year incidence of metastasis than those with low-WHR [**Fig. 1**; RD, 4.3%; 95% confidence interval (CI), 2.2–6.5]. Estimates of the relationship between obesity and 5-year risk of metastasis were attenuated when using obesity defined by BMI (RD, 3.0%; 95% CI, 0.8–5.3). We also

Table 2. 5-year risk and risk differences for the association between WHR-defined obesity and distant metastasis.

	Low WHR risk (*n*)	High WHR risk (*n*)	Risk difference % (95% CI)
Overall[a]	6.9% (1,434)	11.2% (1,333)	+4.3% (2.2–6.5)
Stratified by race[b]			
Non-Black	5.7% (844)	8.5% (566)	+2.8% (0.1–5.5)
Black	8.6% (590)	13.2% (766)	+4.6% (1.3–8.0)
Stratified by PAM50 risk of recurrence (ROR)[a]			
Low/intermediate	5.9% (532)	7.3% (483)	+1.5% (−1.5–4.4)
High	13.1% (155)	26.2% (151)	+13.1% (4.3–21.9)
Stratified by PAM50 subtype[c]			
Non-Basal-like	6.1% (520)	9.2% (478)	+3.1% (0.0–6.2)
Basal-like	14.2% (183)	21.3% (172)	+7.2% (−1.4–15.7)

[a]Adjusted for age, grade, stage, ER status, and race.
[b]Adjusted for age, grade, stage, and ER status.
[c]Unadjusted sensitivity analysis.

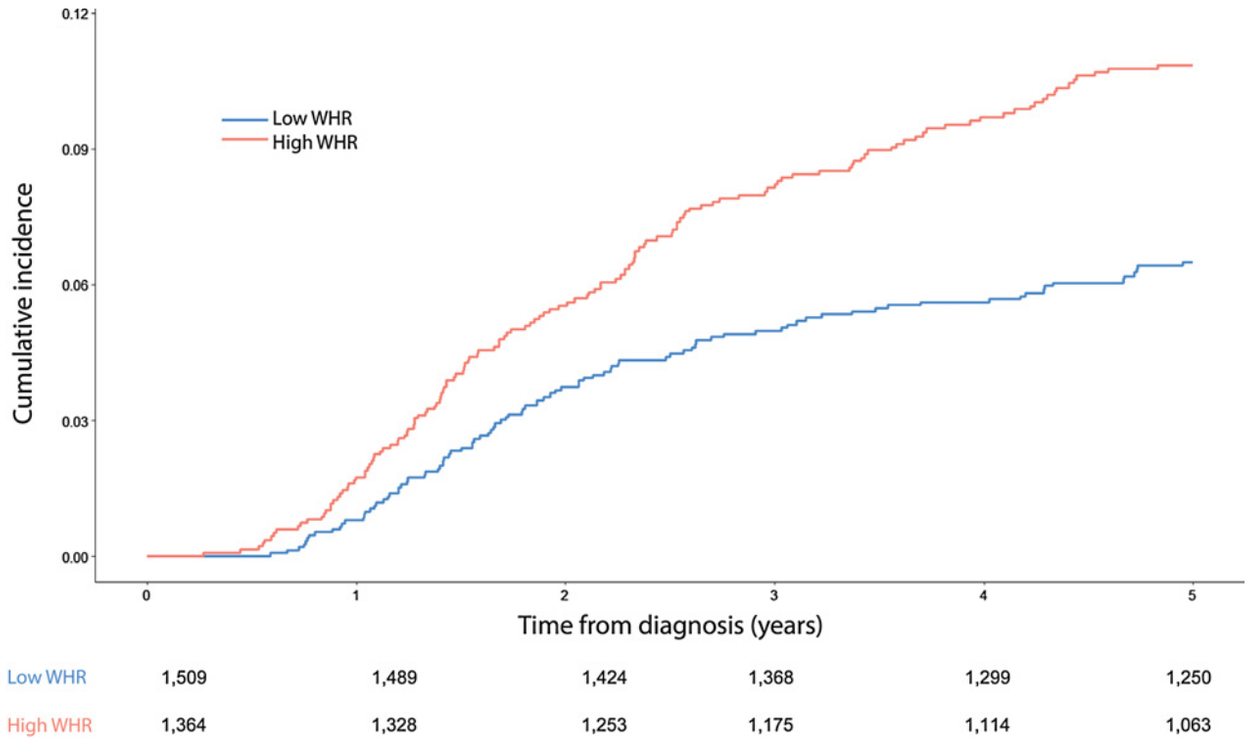

Figure 1.

5-year risk of metastasis by waist-to-hip ratio-defined obesity status. Women who were categorized as obese based on their waist-to-hip ratio experienced significantly shorter time-to-event and higher 5-year risk of metastasis than women with low WHR. The 5-year risk of metastasis among women with high WHR was approximately 4.3 percentage points higher than among women with low WHR (RD, 0.043; 95% CI, 0.022–0.065).

confirmed overall associations between race or ROR and metastasis. In unstratified analyses, Black women experienced significantly more metastases than non-Black women (Supplementary Table S1, R_{Black}: 11.2%, $R_{non\text{-}Black}$: 6.9%), as did women with tumors classified as high ROR (compared with those with low- or intermediate-risk tumors, Supplementary Table S1, R_{High}: 19.5%, $R_{Low\text{-}Int}$: 6.6%).

The relationship between WHR and metastasis also varied over levels of both race and ROR genomic assay scores (**Table 2**). Non-Black, low-WHR women experienced the lowest incidence of metastasis (5.7%), whereas Black, high-WHR women experienced the highest (13.2%). When stratifying the association between WHR and metastasis by race, we observed that the association between WHR and metastasis was stronger among Black women as compared with non-Black women (**Fig. 2**; RD_{Black}, 4.6%; 95% CI, 1.3–8.0; $RD_{non\text{-}Black}$, 2.8%; 95% CI, 0.1–5.5). Similarly, among women with low or intermediate ROR scores, high-WHR and low-WHR women had similar risk of metastasis, with no statistically significant difference (**Fig. 3**; $RD_{Low\text{-}Int}$, 1.5%; 95% CI, −1.5–4.4); however, among women in the high ROR category, high-WHR women had substantially higher incidence of metastasis (**Fig. 3**; RD_{High}, 13.1%; 95% CI, 4.3–21.9). Considering BMI, we did not observe significant differences in incidence of metastasis between obese and non-obese women within strata of ROR categories (BMI RD_{High}, 2.0%; 95% CI, −6.4–10.4); $RD_{Low\text{-}Int}$, 0.5%; 95% CI, –2.6, 3.6) or race (BMI RD_{Black}, 1.0%; 95% CI, −2.4–4.5; $RD_{non\text{-}Black}$, 2.8%; 95% CI −0.2–5.7).

We also performed a sensitivity analysis in which we evaluated WHR–metastasis associations using Basal-like versus non-Basal-like subtype to stratify (rather than ROR-PT). The association between WHR and metastasis was imprecise, consistent with the smaller sample size for the cross-section of Basal-like and high ROR-PT categorization, but the directionality was preserved, with greater associations between WHR and metastasis also observed among high-risk Basal-like tumors (**Table 2**, $RD_{Basal\text{-}like}$ = 7.3%; $RD_{non\text{-}Basal\text{-}like}$ = 3.1%).

Differences in metastatic site

We next assessed the frequency of bone, lung, liver, brain, and other metastases among high-WHR and low-WHR participants. Among women who experienced metastasis during 5-year follow-up (n = 239), the most common site of metastasis was bone (n = 112), followed by lung/pleura (n = 95), liver (n = 67), brain (n = 60), and other sites (n = 49). Almost half of these women (n = 112) presented with multiple metastases at diagnosis of metastasis. More metastases were observed among high-WHR women at every site except brain, at which a smaller proportion of metastases were experienced by high-WHR women (**Table 3**). The largest difference in metastasis frequency between high-WHR and low-WHR participants was observed among women with lung metastases (RFD, 2.7%; 95% CI, 1.2–4.2). More occurrences of multiple metastases were also observed among high-WHR women (RFD, 2.3%; 95% CI, 0.7–3.9). The directions of the associations between BMI-derived obesity and site or multiplicity of metastasis were similar to that of WHR; however, point estimates were lower in magnitude.

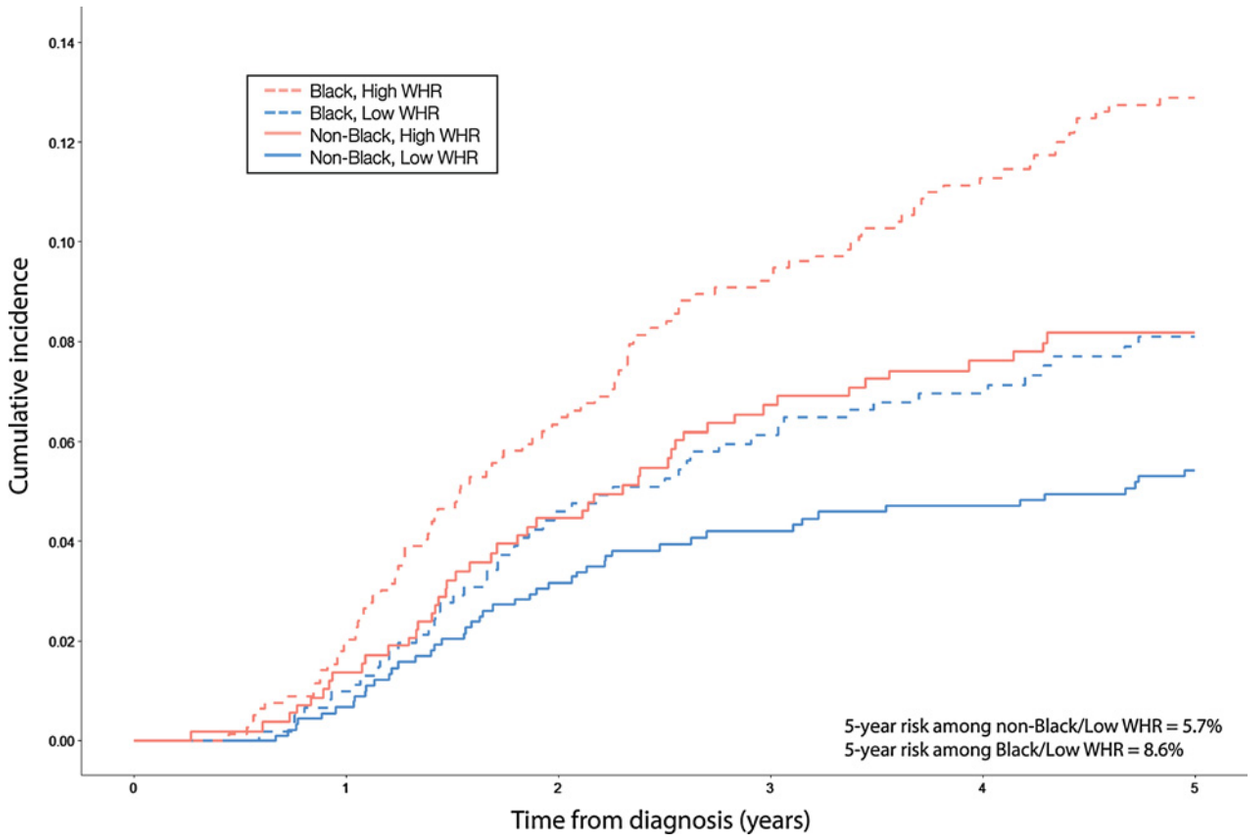

Figure 2.

5-year risk of metastasis by waist-to-hip ratio obesity status, stratified by race. Both overall and stratified by WHR categories, Black women experienced substantially higher rates of metastasis than non-Black women. The association between WHR and 5-year risk of metastasis was evident among both Black and non-Black women, but had a slightly higher magnitude among Black women. [RD among Black women; 0.046 (95% CI, 0.013–0.080); RD among non-Black women, 0.028 (95% CI, 0.001–0.055)].

Discussion

In a large and diverse population-based study, we found that central obesity, as defined by WHR, is associated with higher risk of metastasis among women with stage I–III breast cancer. We also observed that WHR is associated with higher risk of liver, lung, and bone metastases, as well as metastatic multiplicity. The association between WHR and metastasis is particularly strong among women with other high-risk characteristics such as Black race or high ROR score. These findings may help justify targeted interventions among high-WHR women with other high-risk characteristics.

Previous literature has demonstrated a relationship between obesity and both mortality and recurrence (1, 4, 5, 9, 10, 20). Our study is consistent with those reports, demonstrating a positive association between obesity and metastasis. However, many of the previous studies have emphasized BMI, whereas we used WHR, a measure of central adiposity, which may better capture obesity across races (24, 25). Therefore, the results here both display consistency with previous findings and provide insights into an additional measure of obesity associated with breast cancer metastasis. In comparison with BMI, we observed stronger associations between WHR and metastasis, particularly among patients with high-risk tumors. There is limited information about the relationship between obesity and metastasis incorporating genomic data within diverse patient populations. Integrating the tumor molecular characteristics, race, and information on body composition allowed us to pinpoint specific groups of patients in which obesity appears to play a more substantial role, notably those with other aggressive or poor prognostic features.

The site and burden of metastatic lesions has a significant impact on clinical management and prognosis (32, 33). Median survival for patients with brain or liver metastases is lower than for patients with lesions at other distant sites (32, 33). Likewise, patients with multiple metastases have (on average) poorer survival outcomes than those with single metastasis (33). Our findings are consistent with a previous study that observed increased frequency of metastasis among obese or high WHR patients with breast cancer at multiple sites, in particular liver and lung (34). This retrospective study of 118 hospital patients observed that obese women experienced significantly shorter distant metastasis-free survival than their non-obese counterparts and developed earlier visceral (i.e., liver and lung) metastases (34). The results from the same study also suggested an attenuated and non-significant increase in bone and brain metastases among obese patients. However, another retrospective cohort study observed that obese patients did not have increased frequency of metastasis at any site, although the number of patients under study was low, so additional inquiry is warranted (35). Here, we did not observe a significant association between WHR and brain metastases; in fact, among women who

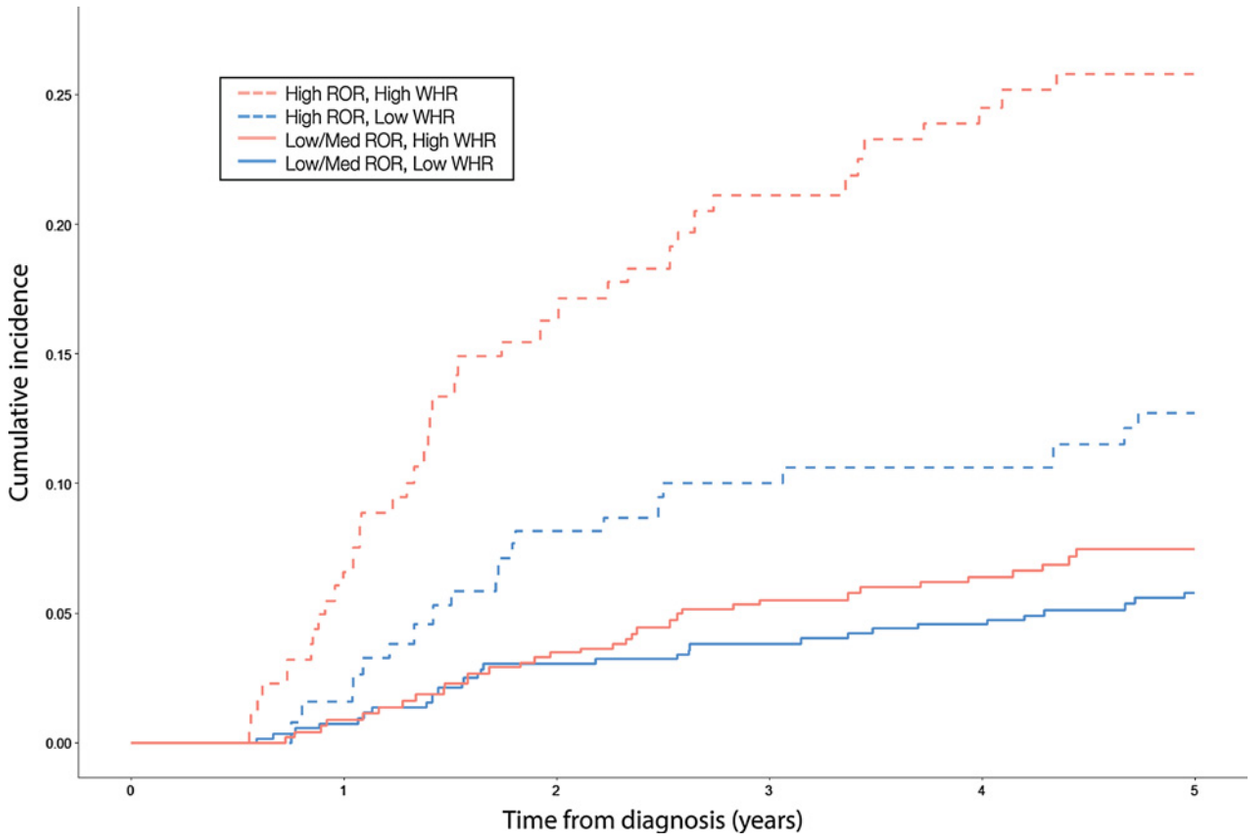

Figure 3.

5-year risk of metastasis by waist-to-hip ratio obesity status, stratified by molecular intrinsic risk score. Among women with available gene expression data ($n = 1,321$), women with high WHR with tumors categorized as having a high molecular risk of recurrence were far more likely to experience a metastasis within 5 years than women with low WHR with high-risk tumors (RD, 0.131; 95% CI, 0.043–0.219). There was little evidence for a risk difference between WHR categories among women with low or intermediate-risk tumors (RD, 0.015; 95% CI, −0.015–0.044).

experienced metastasis, women with low WHR had a higher burden of brain metastasis than women with high WHR.

CBCS3 is a large and diverse prospective cohort of women with incident breast cancer, which allowed us to assess both the relationship between WHR and metastasis, as well as modification of this association by race and genomic assays. Our analysis emphasized 5-year distant metastasis, an outcome that is important as an intermediate for survival and as an independent outcome. However, our analysis also had limitations. In our study, WHR was measured at diagnosis by trained nurse interviewers rather than estimated by self-report, minimizing the risk of misclassification bias. However, anthropometric measurements were only available at baseline, on average five months after diagnosis, so we were not able to look at changes in WHR over time. We were unable to evaluate how associations between obesity and metastatic site varied as a function of tumor subtype due to limited sample size within strata. Previous studies have shown relationships between tumor subtype and metastatic site (e.g., $HER2^+$ tumors associated with brain metastases). However, we do not expect our results for WHR and metastatic site to be confounded by HER2 status because the prevalence of $HER2^+$ tumors did not vary in association with WHR. Finally, we did not explore race-specific cutoff points for WHR, and there may be differences in body composition associated with race that are not adequately addressed using the WHO cutoff point of 0.85.

Metastasis strongly affects patients' physical, emotional, mental, and financial health, and therefore it is important to understand

Table 3. Relative frequency differences for metastasis at each site by WHR-defined obesity status.

Site	High WHR	Low WHR	RFD (95% CI)
Liver	3.5%	2.0%	+1.5% (0.2–2.8)
Lung	5.4%	2.7%	+2.7% (1.2–4.2)
Bone	6.1%	3.7%	+2.5% (0.9–4.1)
Brain	2.7%	2.1%	+0.6% (−0.5–1.8)
Multiple	5.8%	3.6%	+2.3% (0.7–3.9)

modifiable factors that influence metastasis risk. Our findings suggest that obesity may play an important role in progression to metastasis, particularly among patients with other high-risk tumor features and high WHR may be an important indicator alongside clinical characteristics for identification of high-risk patients.

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Authors' Contributions

L.T. Olsson: Conceptualization, software, formal analysis, investigation, visualization, methodology, writing–original draft, writing–review and editing. **A. Walens:** Conceptualization, supervision, investigation, writing–original draft, project administration, writing–review and editing. **A.M. Hamilton:** Data curation, formal analysis, validation, writing–review and editing. **J.M. Fleming:** Conceptualization, investigation, writing–review and editing. **L.A. Carey:** Writing–review and editing. **S.D. Hursting:** Conceptualization, supervision, investigation. **K.P. Williams:** Conceptualization, supervision, writing–review and editing. **M.A. Troester:** Conceptualization, resources, supervision, funding acquisition, methodology, project administration, writing–review and editing.

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Note

Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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