Review article

Obesity and Breast Cancer: Do Age, Race and Subtype Matter?

Kimberly M Arnold[1,2], Nicole J. Flynn[1,3] and Jennifer Sims-Mourtada[1,2,3*]

[1]Center for Translational Cancer Research, Helen F Graham Cancer Center and Research Institute, Christiana Care Health Services, Inc. Newark, USA

[2]DE and Departments of Medical Laboratory, USA

[3]Biological Sciences, The University of Delaware, Newark, DE, USA

Abstract

Obesity rates within the United States are on the rise. Obesity is a known risk factor for various diseases, including cancer. Numerous studies have linked obesity to the incidence and treatment outcomes of breast cancer. However, the risk of obesity may vary between breast cancer subtypes and different racial or age groups. In this article, we review the literature regarding the impact of obesity on incidence and response for different subtypes of breast cancer within different population groups.

Introduction

Over a third of adults in the United States are classified as obese and this number is rising with each passing year [1]. The impact of obesity on the healthcare system is being realized, particularly for women, with obesity related disease responsible for close to 1 in 4 deaths in US women [2]. Although obesity affects all races, the prevalence of obesity in African American women is almost twice that of non-Hispanic white women [3]. Annual age-standardized incidence rates of obesity-related cancers are increasing, with excess weight being associated to 8% of cancers in women from developed countries [4]. High body mass index (BMI) ($>30kg/m^2$) has been directly linked to increased risk and poor outcomes for many cancers, including breast cancer.

Breast cancer is a heterogenous disease composed of histopathological subtypes categorized by expression of the estrogen (ER) and progesterone (PR), HER2 receptor (HER2), or lack thereof (triple negative, TNBC). ER+ cancers represent about 60-70% of all breast cancers. The TN subtype is less common making up about 10-15% of breast cancers diagnosed within the US. TNBC occurs more often in premenopausal and African American women and is associated with high-grade tumors and poorer outcomes than ER+ tumors [5,6]. Likewise, the HER2+ subtype represents about 10% of breast cancers and is characterized by high grade tumors and poor outcomes [6].

Obesity and Breast Cancer Incidence

Although obesity has been linked to development of breast cancer, there are a variety of factors which influence this association, including menopausal status, race, and distribution of adiposity. These factors may also influence the subtype of breast cancer which develops: ER+, TN, or HER2+.

Multiple studies found obese premenopausal women have a reduced risk of breast cancer, indicated by risk ratios (RR) of 0.86 [7] and 0.55 [8] and an increased risk of breast cancer in postmenopausal women (RR 1.27) [8]. Additionally, breast cancer subtypes show differing degrees of correlation with obesity. A study analyzed breast cancer subtype incidence related to risk factors including high BMI and waist-to-hip ratio (WHR) among both African American and white women from the Carolina Breast Cancer Study (CBCS) [9]. Breast cancer subtypes were defined as basal like (ER-, PR-, HER2-), luminal B (ER+, PR+, HER2+), and HER2+/ER- and were compared to luminal A breast cancer (ER+, PR+, HER2-) [9]. Compared to luminal A, women with basal-like breast cancers were more likely to have a BMI ≥30 in premenopausal women, indicated by an odds ratio (OR) of 1.6, but no difference was found in postmenopausal women [9]. Both pre and postmenopausal women with luminal B breast cancer were less likely to have a high BMI (≥ 30) than women with luminal A breast cancer (OR 0.7) [9]. Premenopausal women with HER2+/ER- breast cancer were also less likely to have a high BMI than women with luminal A breast cancer (OR 0.6), but this held little association in postmenopausal women (OR 1.1) [9]. Interestingly, women with basal-like breast cancers were more likely to have high WHR (≥ 0.84) regardless of whether they were premenopausal (OR 1.9) or postmenopausal (OR 1.4) [9]. Therefore, menopausal status and distribution of adiposity (high BMI or WHR) appear to play a role in the varying incidence of breast cancer subtype.

Not only does menopausal status and distribution of adiposity relate to differing incidence of breast cancer subtypes, but race may also play a role. It is established that African American women are

Citation: Kimberly M Arnold, Nicole J. Flynn and Jennifer Sims-Mourtada (2016) Obesity and Breast Cancer: Do Age, Race and Subtype Matter?. BAOJ Cancer Res Ther 2: 021.

Page 2 of 4

already more likely to develop TN tumors than European-American women [10], but the impact of obesity in this relationship is still being elucidated. The AMBER Consortium studied the relationship between obesity and breast cancer subtypes in African American women, related to recent or young adult BMI and WHR [11]. The study found a negative correlation between high BMI ($\geq$ 30) as a young adult and ER+ breast cancer (OR 0.65), and no association between high BMI as a young adult and ER- or TN breast cancer (ER- OR 0.97; TN OR 1.08) [11]. Additionally, high BMI as a young adult ($\geq$ 30) was negatively correlated with breast cancer of all subtypes in post-menopausal women (ER+ OR 0.68; ER- OR 0.78; TN OR 0.77) [11]. Recent high BMI ($\geq$ 35) was associated with an increased risk of ER+ breast cancer in women who were thin as young adults (BMI $\leq$ 19.48) (OR 1.91) and decreased risk of ER- breast cancer in post-menopausal women with a recent high BMI, regardless of BMI as a young adult [11]. Interestingly, a positive correlation was found between recent high WHR ($\geq$ 0.88) and ER+ breast cancer (OR 1.35), and no association was found between high WHR and ER- (OR 1.12) or TN breast cancer in premenopausal women [11]. Alternatively, high WHR was positively correlated with ER+ (OR 1.24), ER- (OR 1.31) and most prominently TN breast cancer (OR 1.73) in post-menopausal women [11]. Overall, breast cancer subtype incidence in both African American and white women differs depending on a variety of factors, including definition of obesity (BMI or WHR), menopausal status, and recent or young adult obesity.

Obesity and Breast Cancer Outcomes

It has long been known that obesity has a negative influence on breast cancer recurrence and survival [12-17]. Meta-analysis of the current literature on the effect of obesity on breast cancer outcomes has revealed worse overall and breast cancer specific survivals in obese women diagnosed with breast cancer compared to non-obese women [14,18]. Large population based cohort studies also show that obesity can increase breast cancer mortality [19-20]. A majority of studies define obesity as a BMI $\geq$ 30. Widschwendter et al. [21] further categorized obesity into slightly (30-34.9), moderately (35-39.9), and severely obese (BMI$\geq$40) and compared each group to non-obese women. Only severely obese women diagnosed with breast cancer had a significantly worse overall and disease free survival compared to those with a normal BMI. Breast cancer patients considered slightly or moderately obese did not have significant differences in survival when compared to patients with a normal BMI [21]. On the other hand, Berclaz et al. [12] showed women diagnosed with breast cancer with a BMI$\geq$25 had worse overall and disease-free survivals compared to women with BMI$\leq$25, however, women with a high BMI had high rates of non-breast cancer death. When bodyweight is used instead of BMI, a trend exists between increasing body weight and breast cancer mortality only in women diagnosed with early stage breast cancer, with high bodyweight having no adverse effect on outcome in women with advanced stage disease [22].

Populations utilized in a majority of studies investigating obesity and breast cancer outcomes tend to consist of postmenopausal women, which usually have advanced stage disease at diagnosis and poorer outcomes [14,23]. Limited studies comparing pre- and postmenopausal women diagnosed with breast cancer reveal obese premenopausal women have worse progression free survival and overall survival compared to obese postmenopausal women [12,24-26]. However, other studies have shown that obesity significantly increases breast cancer mortality and rate of recurrence regardless of menopausal status [27-30]. In addition, it has been shown that there are variations in breast cancer outcomes between ethnicities; however, there is limited data on the effects of obesity on breast cancer outcomes in ethnically diverse populations. Comparisons of women of African, Hispanic, and Asian ancestry in the United States diagnosed with breast cancer have shown that there is an adverse effect of obesity on breast cancer survival in women of Asian descent with similar survival rates between African Americans and Hispanics and non-Hispanic whites [31]. However other studies have shown no effect of race on outcome. Investigation of a cohort of ethnically diverse postmenopausal women found that obese women had a higher risk of overall and breast cancer specific mortality with ethnic differences not having an effect on mortality [32]. In addition, Maskarinec et al. [33] found that survival in obese women diagnosed with breast cancer from ethnically diverse backgrounds have similar survival rates. An investigation done by Dignam et al. [34] on obesity and race on prognosis of women diagnosed with ER negative breast cancer revealed that, after adjusting for BMI, African-American women had worse disease free survival and a higher risk of non-breast cancer death compared to Caucasian women, however, death due to breast cancer was similar between both populations. Further studies comparing age, race, obesity, and breast cancer outcomes need to be completed in larger cohorts before conclusions can be made.

Numerous studies have shown that obesity either before or after diagnosis is associated with poorer survival when all breast cancer subtypes are combined [18,27,32,35-37]. However, investigating the effect of obesity on prognosis of the different breast cancer subtypes produces mixed findings. Obesity in women with ER positive breast cancer did not affect the risk of recurrence or breast cancer mortality but was associated with increased risk of contralateral breast cancer, other primary cancers, and overall mortality [16,34]. However, other studies have shown no significant association between ER status and BMI [23]. In addition, Pajares et al. [38] showed that the negative effect of obesity on outcome was similar across breast cancer subtypes (ER/PR positive/HER2 negative, HER2+, and TNBC). Triple-negative breast cancer is considered to be an aggressive subtype and is typically associated with poor outcome; however, the association between obesity and outcome in women diagnosed with triple negative breast cancer is inconsistent. Dawood et al. [39] showed no difference in women with stage I-III TNBC in disease-free and overall survivals across BMIs at diagnosis. In addition, two other studies showed no association between BMI at diagnosis and TNBC prognosis [40-41]. Interestingly, women with TNBC who were obese a year before diagnosis had worse overall survival and recurrence/disease-specific survival when compared to normal weight women and this

Citation: Kimberly M Arnold, Nicole J. Flynn and Jennifer Sims-Mourtada (2016) Obesity and Breast Cancer: Do Age, Race and Subtype Matter?. BAOJ Cancer Res Ther 2: 021.

Page 3 of 4

appeared stronger in premenopausal women [42-43]. However, obesity at the time of diagnosis or six months post-diagnosis had no association with outcome [42]. In addition, a study to investigate the effects of BMI on the survival of women with differing subtypes of breast cancer showed that women with TNBC who were severely obese (BMI≥40) had significantly worse overall and disease-free survival compared to normal weight women. However, women with a BMI of 30-39.9 who were diagnosed with TNBC did not have significantly worse outcomes. In patients with luminal A-like, luminal B-like, and HER2-positive breast cancer, BMI had no significant effect on survival [21].

Many studies have shown an association between obesity and overall survival [12-17]. However, discrepancy lies in the association between BMI and disease-free survival. Some studies have shown that obese breast cancer patients have worse disease-free survival [13,15,17,44]. However other studies have reported no association between obesity and disease-free survival [12,16,45]. In a study done by Ewertz et al. [23], they separated estimates for the development of locoregional or distant metastasis in comparison to BMI. They found no association between BMI and the development of locoregional metastasis; however 5 to 10 years after diagnosis, the risk of developing distant metastasis increased 46% for patients with a BMI higher than 25 kg/m^2. Conversely, other studies have shown no association between BMI and development of local recurrence and/or distant metastasis [17,46]. Conversely, Marret et al. [46] found that the risk of developing local recurrence was actually less in obese patients, however, this study had a limited number of patients. Interestingly, when you break down levels of obesity and look at patients with BMI ≥ 35, they had a significantly higher risk of recurrence compared to patients with a BMI ≤ 25 however patients with a BMI between 30-35 had similar prognosis as normal weight individuals [38].

Conclusion

Although a general link between obesity and breast cancer incidence and survival is apparent, the impact of obesity may differ between the subtypes of breast cancer. Likewise, the role of obesity among different races or age groups is still uncertain. Development of breast cancer is a complex process that involves numerous genetic and cellular changes, many of which may be altered by obesity at different times over the life of the patient. Understanding the role that obesity plays during breast cancer development and treatment within specific racial or age groups may help to improve population specific guidelines regarding obesity and breast cancer risks. A major issue for data interpretation study comparison is the definition of obesity, which varies significantly from study to study. Until a standardized method is accepted, questions remain about the role obesity plays within different populations and different tumor types.

Acknowledgements

References

1. Ogden CL, Carroll MD, Kit BK, Flegal KM (2013) Prevalence of obesity among adults: United States, 2011-2012. NCHS Data Brief (131):1-8.

2. Masters RK, Reither EN, Powers DA, Yang YC, Burger AE, et al. (2013) The impact of obesity on US mortality levels: the importance of age and cohort factors in population estimates. Am J Public Health 103(10): 1895-1901.

3. Flegal KM, Carroll MD, Kit BK, Ogden CL (2012) Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 307(5): 491-497.

4. Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA et al. (2014) Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol 16(1): 36-46.

5. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, et al. (2007) The triple negative paradox: primary tumor chemo sensitivity of breast cancer subtypes. Clin Cancer Res 13(8): 2329-2334.

6. Blows FM, Driver KE, Schmidt MK, Broeks A, van Leeuwen FE, et al. (2010) Sub typing of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 cases from 12 studies. PLoS Med 7(5): e1000279.

7. Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, et al. (2012) Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis 159(9): 635-648.

8. van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, et al. (1999) Pooled Analysis of Prospective Cohort Studies on Height, Weight, and Breast Cancer Risk 152(6) :514-527.

9. Millikan RC, Newman B, Tse CK, Moorman PG, Conway K, et al. (2008) Epidemiology of basal-like breast cancer 109(1): 123-139.

10. Amed K, Hicks D, Ambrosone CB (2006) Breast Cancer in African-American Women: Differences in Tumor Biology from European-American Women. Cancer Res 66(17): 8327-8330.

11. Bandera EV, Changran U, Hong CC, Troester MA, Bethea TN, et al. (2015) Obesity, body fat distribution, and risk of breast cancer subtypes in African American women participating in the AMBER Consortium. Breast Cancer Res Treat 150(3): 655-666.

12. Berclaz G, Li S, Price KN, Coates AS, Castiglione-Gertsch M, et al. (2004) Body mass index as a prognostic feature in operable breast cancer: The International Breast Cancer Study Group experience. Ann Oncol 15: 875-884.

13. Chen X, Lu W, Zheng W, Gu K, Chen Z,et al. (2010) Obesity and weight change in relation to breast cancer survival. Breast Cancer Res Treat 122: 823-833.

14. Chlebowski RT, Aiello E, McTiernan A (2002) Weight loss in breast cancer management. J Clin Oncol 20:1128-1143.

15. de Azambuja E, McCaskill-Stevens W, Francis P, Quinaux E, Crown JP, et al. (2010) The effect of body mass index on overall and disease-free survival in node-positive breast cancer patients treated with docetaxel and doxorubicin-containing adjuvant chemotherapy: The experience of the BIG 02-98 trial. Cancer Res Treat 119:145-153.

Citation: Kimberly M Arnold, Nicole J. Flynn and Jennifer Sims-Mourtada (2016) Obesity and Breast Cancer: Do Age, Race and Subtype Matter?. BAOJ Cancer Res Ther 2: 021.

Page 4 of 4

16. Dignam JJ, Wieand, K, Johnson KA, Fisher B, Xu L, et al. (2003) Obesity, tamoxifen use, and outcomes in women with estrogen receptor-positive early-stage breast cancer. J Natl Cancer Inst 95: 1467-1476.

17. Majed B, Moreau T, Senouci K, Salmon RJ, Fourquet A, et al. (2008) Is obesity an independent prognosis factor in woman breast cancer? Breast Cancer Res Treat 111: 329-342.

18. Protani M, Coory M, Martin JH (2010) Effect of obesity on survival of women with breast cancer: systemic review and meta-analysis. Breast Cancer Res Treat 123: 627-635.

19. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ (2003) Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. N Engl J Med 348 (17): 1625-1638.

20. Reeves GK, Pirie K, Beral V, Green J, Spencer E, et al. (2007) Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study Br Med J 335 (7630):1134-1139.

21. Widschwendter P, Friedl TWP, Schwentner L, DeGregorio N, Jaeger B, et al. (2015) The influence of obesity on survival in early, high-risk breast cancer: results from the randomized SUCCESS A trial. Breast Cancer Research 17:129.

22. Enger SM, Greif JM, Polikoff J, Press M (2007) Bodyweight correlates with mortality in early-stage breast cancer. Arch. Surg 139 (9): 954-958.

23. Ewertz M, Jensen M-B, GunnarsdottirKAm, Højris I, Jakobsen EH, et al. (2011) Effect of obesity on prognosis after early-stage breast cancer. J ClinOncol 29:25-31.

24. Daling JR, Malone KE, Doody DR, Johnson LG, Gralow JR, et al. (2001) Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. Cancer 92(4):720-729.

25. Holmberg L, Lund E, Bergstrom R, Adami HO, Meirik O (1994) 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 30A: 351-354.

26. Osman MA, Hennessy BT Obesity (2015) correlation with metastases development and response to first-line metastatic chemotherapy in breast cancer. Clinical medicine insights Oncology 9:105-112.

27. Chan DS, Vieira AR, Aune D, E. V. Bandera, D. C. Greenwood, et al. (2014) Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. Ann Oncol 25:1901–1914.

28. Cleveland RJ, Eng SM, Abrahamson PE, Britton JA, Teitelbaum SL, et al. (2005) Weight gain prior to diagnosis and survival from breast cancer. Cancer Epidemiol. Biomarkers Prev 16 (9): 1803-1811.

29. Dawood S, Broglio K, Gonzalez-Angulo AM, Kau SW, Islam R, et al. (2008) Prognostic value of body mass index in locally advanced breast cancer. Clin. Cancer Res 14(6): 1718-1725.

30. Whiteman MK, Hillis SD, Curtis KM, McDonald JA, Wingo PA, et al. (2005) Body mass and mortality after breast cancer diagnosis. Cancer Epidemiol Biomarkers Prev 14(8) : 2009-2014.

31. Bandera EV, Maskarinec G, Romieu I, John EM (2015) Racial and ethnic disparities in the impact of obesity on breast cancer risk and survival: a global perspective Adv Nutr 6(6): 803-819.

32. Conroy SM, Maskarinec G, Wilkens LR, White KK, Henderson BE, et al. (2011) Obesity and breast cancer survival in ethnically diverse postmenopausal women: the Multiethnic Cohort Study. Breast Cancer Res Treat 129:565–574.

33. Maskarinec G, Pagano I, Lurie G, Bantum E, Gotay CC, et al. (2011) Factors affecting survival among women with breast cancer in Hawaii. J Womens Health (Larchmt) 20(2) :231-237.

34. Dignam JJ, Wieand K, Johnson KA, Raich P, Anderson SJ, et al. (2006) Effects of obesity and race on prognosis in lymph node-negative, estrogen receptor-negative breast cancer. Breast Cancer Res Treat 97(3): 245-254.

35. Azrad M, Demark-Wahnefried W (2014) The association between adiposity and breast cancer recurrence and survival: a review of the recent literature. Curr Nutr Rep 3 :9–15.

36. Jiralerspong S, Kim ES, Dong W, Feng L, Hortobagyi GN, et al. (2013) Giordano SH. Obesity, diabetes, and survival outcomes in a large cohort of early-stage breast cancer patients. Ann Oncol 24: 2506–2514.

37. Kwan ML, Chen WY, Kroenke CH, Weltzien EK, Beasley JM, et al. (2012) Pre-diagnosis body mass index and survival after breast cancer in the After Breast Cancer Pooling Project. Breast Cancer Res Treat 132:729–739.

38. Pajares B, Pollan M, Martin M, Mackey JR, Lluch A, et al. (2013) Obesity and survival in operable breast cancer patients treated with adjuvant anthracyclines and taxanes according to pathological subtypes: a pooled analysis. Breast Cancer Res 15: R105.

39. Dawood S, Lei X, Litton JK, Buchholz TA, Hortobagyi GN, et al. (2012) Impact of body mass index on survival outcome among women with early stage triple-negative breast cancer. Clin Breast Cancer 12: 364–372.

40. Ademuyiwa FO, Groman A, O'Connor T, Ambrosone C, Watroba N, et al. (2011) Impact of body mass index on clinical outcomes in triple-negative breast cancer. Cancer 117: 4132–4140.

41. Tait S, Pacheco JM, Gao F, Bumb C, Ellis MJ, et al. (2014) Body mass index, diabetes, and triple-negative breast cancer prognosis. Breast Cancer Res Treat 146:189–197.

42. Bao P-P, Cai H, Peng P, Gu K, Su Y, Shu X-O, et al. (2016) Body mass index and weight change in relation to triple-negative breast cancer survival. Cancer Causes Control 27(2) : 229-236.

43. Turkoz FP, Solak M, Petekkaya I, Keskin O, Kertmen N, et al. (2013) The prognostic impact of obesity on molecular subtypes of breast cancer in premenopausal women. J BUON 18:335–341.

44. Senie RT, Rosen PP, Rhodes P, Lesser ML, Kinne DW, et al. (1992) Obesity at diagnosis of breast carcinoma influences duration of disease-free survival. Ann Intern Med 116: 26–32.

45. Katoh A, Watzlaf VJ, D'Amico F (1994) An examination of obesity and breast cancer survival in post-menopausal women. Br J Cancer 70(5): 928-933.

46. Marret H, Perrotin F, Bougnoux P, Descamps P, Hubert B, et al. (2001) Low body mass index is an independent favor of local recurrence after conservative treatment of breast cancer. Breast Cancer Res Treat 66(1): 17-23.