OXFORD

JNCI J Natl Cancer Inst (2021) 113(2): djaa091

doi: 10.1093/jnci/djaa091
First published online July 6, 2020
Editorial

Obesity and Breast Cancer: Expanding the Hypothesis Space

Ana Elisa Lohmann, MD, PhD,[1] Pamela J. Goodwin, MD, MSc, FRCPC[2,*]

[1]Department of Oncology, London Health Sciences Centre, University of Western Ontario, London, Ontario, Canada and [2]Department of Medicine, Lunenfeld Tanenbaum Research Institute at Mount Sinai Hospital, University of Toronto, Ontario, Canada

*Correspondence to: Pamela J. Goodwin, MD, MSc, FRCPC, Lunenfeld Tanenbaum Research Institute at Mount Sinai Hospital, University of Toronto, 1085-600 University Avenue, Toronto, ON M5G 1X5, Canada (e-mail: Pamela.Goodwin@sinaihealthsystem.ca).

Obesity is adversely associated with breast cancer (BC) risk (particularly in postmenopausal women) and with BC prognosis (1, 2). In a meta-analysis, our group showed that women who were obese at BC diagnosis had a higher risk of total mortality and mortality from BC, regardless of their menopausal status, when compared with normal weight women; the summary relative risk of total mortality was 1.35 (95% confidence interval [CI] = 1.24 to 1.47) and 1.35 (95% CI = 1.24 to 1.47; 22 studies) for mortality from BC (3). More recently, in a literature-based meta-analysis, we reported that the pooled hazard ratios (HRs) for disease-free survival and overall survival (OS) in obese vs nonobese were worse in all immunohistochemically defined BC subtypes, although prognostic effects were smaller in the triple-negative subtype (HR = 1.23, 95% CI = 1.08 to 1.40; $P = .002$) for OS and a HR of 1.15 (95% CI = 1.05 to 1.26; $P = .03$) for disease-free survival (4).

Given the aggressiveness of triple-negative BC (TNBC), prognostic and predictive markers that could guide development of future targeted interventions have been sought. The presence of stromal tumor-infiltrating lymphocytes (sTILs) in TNBC has been identified as a prognostic factor and also as a predictor of response to chemotherapy (5) and immunotherapy (6).

In this issue of the Journal, Floris et al. (7) evaluate the impact of body mass index (BMI) at diagnosis on the association of sTILs with outcomes in TNBC patients receiving neoadjuvant chemotherapy. Although BMI was not associated with the extent of sTILs (measured categorically or continuously), there was a statistically significant interaction of BMI with the association of sTILs and pathologic complete response (pCR); higher levels of sTILs (measured categorically as >30% vs <30%, or continuously) were statistically significantly associated with higher pCR. Higher sTILs were also associated with statistically significantly better event-free survival and OS in lean (BMI $< 25\ kg/m^2$) but not in overweight or obese (BMI $> 25\ kg/m^2$) individuals. These observations provide evidence of an impact of obesity (as reflected by BMI) on the association of sTILs with chemotherapy response and outcomes in TNBC.

Interestingly, a similar BMI-related pattern has been seen by Barba et al. (8), who studied the impact of BMI on the association of phosphorylated γ-H2X, which is formed as a repair mechanism in response to DNA double-strand breaks, with pCR in TNBC. Higher levels of γ-H2AX (potentially reflecting enhanced DNA repair leading to chemotherapy resistance) were associated with reduced pCR in lean subjects but not in obese individuals. The authors discussed obesity-associated metabolic changes (eg, higher insulin and glucose, altered adipokines) and/or increases in oxidative stress leading to greater DNA damage as potentially contributing to this BMI effect.

What does the loss (or reduction) of a beneficial effect of high sTILs in overweight or obese individuals with TNBC who are receiving chemotherapy tell us? In considering this question, it is important to note that the interaction reported by Floris et al. (7) was quantitative rather than qualitative. That is, high (vs low) sTILs still seemed to be associated with enhanced pCR rates in overweight and obese (45% vs 34%), but the degree of enhancement was less than in lean individuals (73% vs 36%) (7). This may reflect the presence of other inflammatory changes, apart from sTILs, in the tumor microenvironment in overweight and obese patients that were driving tumor growth and reducing response to chemotherapy, reducing effects of sTILs. These changes may include higher levels of inflammatory cytokines, increased infiltration of other inflammatory cells (including macrophages), and/or altered function of inflammatory cells in obese and overweight individuals (9). An alternate explanation could be that changes in systemic physiology in overweight and obese individuals, such as higher insulin and related growth factors, may have stimulated growth of tumor cells directly, reducing chemotherapy response independent of TILs.

In mouse models, obesity appears to be a mediator of immune dysfunction, an effect that is at least partially driven by higher levels of leptin, leading to increased T-cell activation, T-cell dysfunction, and upregulation of PD-1 expression in T cells (10–13). Interestingly, leptin levels are correlated with PD-1 expression on CD8+ T cells ($R = 0.43$; $P = .001$) in healthy obese individuals. A similar pattern has been seen in patients with melanoma where a 1.57-fold increase in mean PD-1 expression in obese vs nonobese has been observed ($P = .019$) (10). These

Received: June 15, 2020; **Accepted:** June 16, 2020

observations suggest a biologic basis for preclinical and clinical reports that obesity is associated with greater tumor responsiveness to checkpoint blockade (10,14,15). In metastatic melanoma patients receiving immunotherapy, obesity (vs normal weight) has been associated with higher OS (HR = 0.54, 95% CI = 0.34 to 0.86) and progression-free survival (HR = 0.63, 95% CI = 0.41 to 0.95) (14). Similar results have been observed in a patient-level meta-analysis of clinical trials with the immune checkpoint inhibitor atezolizumab in metastatic lung cancer; improvement in OS was greatest in obese patients, particularly those with highest PDL-1 expression (HR = 0.36, 95% CI = 0.21 to 0.62) (15).

Because it is unknown whether obesity may affect the response to checkpoint inhibitors in TNBC, analysis of BMI effects in phase III clinical trials involving PD-L1 or PD-1 inhibitors such as atezolizumab in the Impassion130 trial (16) and pembrolizumab in the KEYNOTE- 355 trial (17) is warranted. It would also be important to investigate the addition of checkpoint inhibitors to neoadjuvant chemotherapy in TNBC across BMI categories to determine whether these agents could restore the association of sTILs with response in overweight and obese individuals.

The report by Floris et al. (7) is an important addition to the literature. It underscores the complexity of the contribution of obesity to BC, and it expands the "hypothesis space" regarding potential mechanisms by which obesity may impact BC outcomes. Ideally, the observations reported in this paper will lead to the testing of interventions that will enhance BC outcomes.

Funding

Funded by the Breast Cancer Research Foundation.

Notes

Author contributions: All authors were involved in the writing of this manuscript; all approved the final version of the manuscript.

References

1. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348(17):1625–1638.
2. Chan DS, Vieira AR, Aune D, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol*. 2014;25(10):1901–1914.
3. Niraula S, Ocana A, Ennis M, et al. Body size and breast cancer prognosis in relation to hormone receptor and menopausal status: a meta-analysis. *Breast Cancer Res Treat*. 2012;134(2):769–781.
4. Lohmann AE, Soldera SV, Pimentel I, et al. Association of obesity with breast cancer outcome in relation to cancer subtypes. *J Clin Oncol* . 2019; 37(15_suppl):11557.
5. Denkert C, von Minckwitz G, Darb-Esfahani S, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. *Lancet Oncol*. 2018; 19(1):40–50.
6. Loi S, Winer E, Lipatov O, et al. Abstract PD5-03: Relationship between tumor-infiltrating lymphocytes (TILs) and outcomes in the KEYNOTE-119 study of pembrolizumab vs chemotherapy for 80(4 suppl):PD5-03-PD5-03.
7. Floris G, Richard F, Hamy-Petit A-S, et al. Body mass index and tumor infiltrating lymphocytes in triple-negative breast cancer. *J Natl Cancer Inst*. 2021; 113(2):146–153.
8. Barba M, Vici P, Pizzuti L, et al. Body mass index modifies the relationship between γ-H2AX, a DNA damage biomarker, and pathological complete response in triple-negative breast cancer. *BMC Cancer*. 2017;17(1):101.
9. Gilbert CA, Slingerland JM. Cytokines, obesity, and cancer: new insights on mechanisms linking obesity to cancer risk and progression. *Annu Rev Med*. 2013;64(1):45–57.
10. Wang Z, Aguilar EG, Luna JI, et al. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. *Nat Med*. 2019; 25(1):141–151.
11. Shirakawa K, Yan X, Shinmura K, et al. Obesity accelerates T cell senescence in murine visceral adipose tissue. *J Clin Invest*. 2016;126(12):4626–4639.
12. Bengsch B, Johnson AL, Kurachi M, et al. Bioenergetic insufficiencies due to metabolic alterations regulated by the inhibitory receptor PD-1 are an early driver of CD8(+) T cell exhaustion. *Immunity*. 2016;45(2):358–373.
13. Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. *Nat Rev Endocrinol*. 2017;13(11):633–643.
14. McQuade JL, Daniel CR, Hess KR, et al. Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. *Lancet Oncol*. 2018;19(3):310–322.
15. Kichenadasse G, Miners JO, Mangoni AA, et al. Association between body mass index and overall survival with immune checkpoint inhibitor therapy for advanced non–small cell lung cancer. *JAMA Oncol*. 2020;6(4):512–518.
16. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379(22):2108–2121.
17. Cortes J, Cescon DW, Rugo HS, et al. KEYNOTE-355: randomized, double-blind, phase III study of pembrolizumab + chemotherapy versus placebo + chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer. *J Clinc Oncol*. 2020;38(15_suppl):1000.