The Breast 24 (2015) S56–S59

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Obesity, insulin resistance and breast cancer outcomes

Pamela J. Goodwin [a, b, *]

[a] Department of Medicine, Division of Medical Oncology and Hematology, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada
[b] Division of Clinical Epidemiology, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Available online 15 August 2015

Keywords:
Breast cancer
Adjuvant
Obesity
Aromatase inhibitors
Biology
Intervention

ABSTRACT

There is growing evidence that obesity is associated with poor outcomes in early stage breast cancer. This paper addresses four current areas of focus: 1. Is obesity associated with poor outcomes in all biologic subtypes of breast cancer? 2. Does obesity effect AI efficacy or estrogen suppression in the adjuvant setting? 3. What are the potential biologic underpinnings of the obesity-breast cancer association? 4. Are intervention studies warranted? If so, which interventions in which populations? Research is needed to resolve these questions; intervention trials involving lifestyle interventions or targeting the biology postulated to link obesity and cancer are recommended.

Introduction

There is growing recognition that obesity is associated with adverse breast cancer outcomes, notably a higher risk of distant recurrence and death. Research since St. Gallen 2013 [1] has focused on four key areas – (1) Is obesity associated with poor outcomes in all biologic subtypes of breast cancer?, (2) Does obesity impact aromatase inhibitor (AI) efficacy or estrogen suppression in the adjuvant setting?, (3) What are the potential biologic underpinnings of the obesity-breast cancer outcome association?, and (4) Are intervention studies warranted? If so, which interventions in which populations? These four areas of research will be discussed below.

Is obesity associated with poor outcomes in all biologic subtypes of breast cancer?

Body mass index (BMI) at diagnosis has been associated with both breast cancer mortality and overall mortality in research spanning five decades. In a recent meta-analysis [2], a curvilinear association of BMI with outcome was seen – increased risk was present in individuals with BMI under 20 kg/m^2 and BMI over 25 kg/m^2 at diagnosed – in the latter group, the risk increased with increasing BMI. In a prior meta-analysis [3], obesity was associated with adverse outcome (overall or breast cancer specific mortality) in both pre- and postmenopausal women, in those diagnosed both prior to and after 1995, and in observational cohorts as well as "treatment cohorts" (i.e. retrospective analyses nested in randomized trials) – Hazard ratios (HRs) for obese vs. non-obese overall and in these subgroups were in the range of 1.2–1.35.

Our group [4] performed a meta-analysis of obesity associations in women with estrogen receptor (ER) positive vs. negative breast cancer – hazard ratios (HRs) for breast cancer specific survival (BCSS) and overall survival (OS) were similarly elevated in both groups (BCSS HRs 1.46, 1.36 respectively). However, some recent studies (e.g. Sparano et al.) [5] have found no evidence of an association of obesity with outcome in hormone receptor negative breast cancer. At least ten subsequent studies have explored this issue with varying results. For example, Pajares et al. [6] reported worse BCSS and OS in women having a BMI over 35 kg/m^2 with hormone receptor negative or HER2+ breast cancer enrolled onto a series of randomized trials, all of which involved anthracyclines.

Importantly, Pan et al. [7] analyzed associations of BMI with outcome in over 80,000 women (20,000 ER positive premenopausal, 40,000 ER positive postmenopausal, 20,000 ER negative) enrolled onto randomized trials included in the Early Breast Cancer Clinical Trialists Cooperative Group (EBCTCG). In their patient-level meta-analyses, they found an increased risk of breast cancer mortality in heavier premenopausal women with ER positive breast cancer – HR per 10 kg/m^2 in BMI 1.23 [95% confidence intervals (CIs) 1.16–1.31, $p < 0.00001$], regardless of whether the trial tested hormone, chemotherapy or other treatments. In contrast to earlier

* Mount Sinai Hospital, 1284-600 University Avenue, Toronto, Ontario M5G 1X5, Canada. Tel.: +1 416 586 8605; fax: +1 416 586 8659.
E-mail address: pgoodwin@mtsinai.on.ca.

http://dx.doi.org/10.1016/j.breast.2015.07.014
0960-9776/

study-level meta-analyses, no significant association was seen in postmenopausal women with ER positive breast cancer (HR 1.03, p = 0.27) or in pre- or postmenopausal women with ER negative breast cancer (HR 1.02, p = 0.39).

The basis for these recent discrepancies is not well understood. Because most of the discrepant findings arose from randomized clinical trials (RCTs), one possibility is that women enrolled onto these trials differ from the general population of breast cancer patients with respect to factors, such as metabolic health, that are relevant to the obesity-cancer link. This issue has not been examined in breast cancer patients, however, in the Physicians' Health Study, those who responded to an invitation to be assessed for participation, those willing to be assessed for eligibility, those eligible for randomization, and those who actually accepted randomization had increasingly lower total mortality, cardiovascular mortality and cancer mortality than those who did not meet these criteria. This is evidence of a selection bias (towards enrolment of healthier individuals) occurring during the recruitment process. Furthermore, Kramer et al. [8] have provided evidence that obesity does not necessarily predict metabolic health (defined as no components of the insulin resistance syndrome) – those who are metabolically unhealthy have increased all-cause mortality and cardiovascular events, independent of BMI category (normal weight, overweight or obesity). Thus, it is possible that randomization onto breast cancer clinical trials selects for metabolically healthy individuals, regardless of baseline BMI, either as a direct result of inclusion/exclusion criteria (e.g. a requirement for normal cardiac function in trials of anthracyclines or trastuzumab) or through a more subtle selection of healthy individuals as was seen in the Physicians' Health Study. If so, prognostic associations of BMI may have been obscured.

Does obesity effect AI efficacy or estrogen suppression in the adjuvant setting?

Total body aromatization increases with increasing BMI; leptin and inflammation (both associated with obesity) may also increase aromatase activity independent of BMI. At St. Gallen 2013, the potential effect of baseline BMI on the relative efficacy of AIs vs. tamoxifen in a series of adjuvant trials was discussed [1]. To summarize, in BIG 1-98 [9] (which compared letrozole to tamoxifen) there was no evidence of a significant treatment by BMI interaction. However, in the Anastrozole, Tamoxifen Alone or in Combination (ATAC) [10] and Australian Breast Cancer Study Group (ABCSG) –12 [11] trials (which compared anastrozole to tamoxifen, in postmenopausal women in the former and in combination with goserelin in premenopausal women in the latter), there was evidence that the relative benefit of anastrozole vs. tamoxifen was greatest when BMI was normal vs. elevated. In the ATAC trial [10], this effect of BMI was not statistically significant. In ABSCG-12 [11], disease-free survival (DFS) and OS were worse in women with BMI over 25 kg/m^2 who received anastrozole as opposed to tamoxifen (HR 1.49, 95% CI 0.93–2.0 and HR 3.03, 95%CI 1.35–6.82 respectively). In the TEAM Trial [12] there was no evidence that the relative benefit of exemestane vs. tamoxifen differed across BMI levels. New since St. Gallen 2013 is a report by Gnant et al. [13] which examined the use of extended adjuvant anastrozole vs. no treatment in postmenopausal women – a benefit for anastrozole was seen only in women with baseline BMI <25 kg/m^2 [DFS HR 0.48 (95% CI 0.26–0.89), distant DFS HR 0.22 (95% CI 0.05–1.0), and OS HR 0.45 (95% CI 0.19–1.04)]. No benefit was seen in individuals with a BMI over 25 kg/m^2; the BMI by treatment benefit interaction approached significance for distant DFS (p = 0.07).

Recently, a series of studies [14–18] has examined the extent to which AIs suppress circulating levels of estradiol or estrone according to BMI levels (see Table 1). Folkerd et al. [14] reported that levels of estrone and estradiol were greater at higher levels of BMI in 44 women receiving anastrozole or letrozole – this was statistically significant in those receiving letrozole (r = 0.35, p = 0.013 for estradiol and r = 0.30, p = 0.035 for estrone sulfate) – a non-significant trend was seen in those receiving anastrozole. Of note, levels of both estradiol and estrone sulfate were lower in those receiving letrozole vs. anastrozole across all BMI categories. Pfeiler et al. [15] found a similar pattern of higher estradiol levels in 28 obese (vs. 40. non-obese) women receiving AIs (60 anastrozole, 8 letrozole), r = 0.35, p = 0.05; importantly, FSH levels were lower in obese women (r = 0.34, p = 0.06), consistent with higher endogenous estrogen levels. Kyvernitakis I et al. [17] studied 70 postmenopausal women receiving adjuvant anastrozole; after 12–24 months of treatment, overweight and obese women has non-significantly higher estradiol concentrations than normal weight women. Elliott et al. [18] studied a mixed group of 64 adjuvant and second line patients (who had progressed on an AI) receiving one of the three approved AIs; BMI and estradiol were higher in metastatic patients. BMI was non-significantly correlated with estradiol (9.3% higher for normal vs. overweight vs. obese, p = 0.06). Finally, Lonning et al. [16] reported that treatment levels of estrone sulfate were significantly correlated with BMI in 64 women receiving letrozole or anastrozole in the adjuvant or metastatic setting (n = 25, r = 0.60, p = 0.001 and n = 12, r = 0.61, p = 0.035 respectively). Similar to results of Folkerd et al., [15] estrone sulfate levels were higher in those receiving anastrozole (vs. letrozole), independent of BMI. BMI was not correlated with on-treatment in vivo aromatization in the metastatic setting in women receiving a range of first, second or third line AIs, nor was it correlated with intratumoral levels of estrogens in the neoadjuvant setting. Although many of the reported BMI associations were not statistically significant, sample sizes were small and most studies reported higher estrogen levels in heavier women. Further research employing larger sample sizes is urgently needed.

Although these data suggest estrogen suppression may be less effective in women with higher BMI, there is little evidence that this impacted clinical outcomes in obese women receiving letrozole relative to tamoxifen (BIG 1–98) [9]. There is growing evidence that higher BMI may contribute to reduced efficacy of anastrazole vs. tamoxifen. Because of this, selection of other AIs, notably letrozole, is preferred in overweight or obese women.

What are the potential biologic underpinnings of the obesity-breast cancer association?

There is an evolving understanding of the complex biology potentially underlying the association between obesity and cancer in general, and breast cancer outcomes in particular. A number of recent review articles have addressed this issue in detail [19–21]. Obesity leads to an expanded and reprogrammed, metabolically active, adipose tissue mass, with increased numbers of pre-adipocytes and inflammatory cells, higher levels of leptin and free fatty acids, and greater release of cytokines and other inflammatory compounds. These changes result in an altered systemic physiology, leading to insulin resistance (higher insulin levels, dysglycemia, other metabolic changes), higher circulating levels of free fatty acids, lipids, leptin, estrogens and inflammatory markers. This altered systemic physiology can have direct effects on cancer cells, with higher levels of circulating estrogen, insulin and inflammatory factors activating estrogen and insulin/IGF signaling pathways (e.g. PI3K, ras) as well as JAK-STAT, NF-kappa-β and other pathways. The associated dysglycemia may be associated with altered tumor cell metabolism, such as a shift from oxidative phosphorylation to aerobic glycolysis (the Warburg effect). Locally, adipose cells in the