Triple-negative breast cancer and its association with obesity (Review)

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Abstract. Triple-negative breast cancer (TNBC) is a subtype of breast cancer that lacks expression of the estrogen and progesterone receptor and does not overexpress human epidermal growth factor 2 receptor protein. TNBC is associated with special characteristics, including aggressiveness, poor prognosis and poor response to treatment, and has been attracting increasing attention worldwide. Obesity is a well-documented factor exerting a significant effect on the development of breast cancer, including TNBC. The purpose of the present review was to focus on the association between obesity and TNBC and provide a summary of novel research findings. The aim was to highlight the association between TNBC and obesity and provide an overview of novel outlooks on clinical issues, biological rationale, novel targeted therapies and prognosis, in order to draw attention to the significance of weight management, primary prevention, early diagnosis and treatment of this intractable disease.

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1. Introduction

Breast cancer is the leading cause of cancer-related mortality in women worldwide. According to the data from the International Agency for Research on Cancer, breast cancer alone accounts for 25% of all cancer cases and 15% of all cancer deaths among women (1), which is significantly higher compared with other cancers. The incidence of breast cancer in developing Asian countries has sharply increased, with an expected ~2.5 million breast cancer cases in China by 2021 (2). Studies conducted in the 1970s suggested that obese women were at a higher risk of developing breast cancer (3). According to a systematic review of epidemiological evidence from the American Cancer Research Council, a large number of animal models have demonstrated that overweight status and obesity significantly increase the risk of breast cancer (4).

Triple-negative breast cancer (TNBC), which comprises 10-20% of all breast cancers (5), has recently been described as a special phenotype of breast cancer that lacks expression of estrogen receptor (ER) and progesterone receptor (PR) and does not overexpress the human epidermal growth factor 2 receptor (HER2) protein. Evidence from laboratory and observational studies has suggested that TNBC has a relatively high rate of recurrence and distant metastasis, with poor overall survival (OS) (6). The association between obesity and TNBC has not been fully elucidated. The aim of the present review was to summarize novel, but not yet widely shared outlooks on that intractable disease.

2. Obesity and clinical issues in TNBC patients

A higher proportion of obese patients suffer from TNBC. Body mass index (BMI) has been widely used for diagnosing obesity and for assessing the association between obesity and breast cancer. From a case-only analysis, it was found that women with TNBC were more likely to be overweight or obese [odds ratio (OR)=1.89, 95% confidence interval (CI): 1.22-2.92] (7). Over the last few years, an increasing body of retrospective studies based on population analyses suggests that the incidence of obese TNBC patients is higher compared with that of non-obese patients. A retrospective study investigated 620 Caucasian patients with invasive breast cancer in West Virginia, among whom obesity was present in 49.6% of the

TNBC patients, but in only 35.8% of the non-TNBC patients (P=0.0098) (8). Another study of clinicopathological data obtained from 112 TNBC patients in a Turkish hospital over a 5-year period reported that 30 (26.8%) were normoweight or underweight, and 82 (73.2%) were overweight/obese at the time of diagnosis (9). Similarly, an American scholar from Louisiana reviewed a database of a total of 183 TNBC patients, among whom 24 (13.1%) were normoweight (BMI <25 kg/m^2), 42 (23.1%) were overweight (BMI=25-30 kg/m^2), and 117 (63.7%) were obese (BMI >30 kg/m^2) (10). Ademuyiwa *et al* (11) classified patients based on BMI in a retrospective study and reported that, of 418 TNBC patients over 14 years, 124 (29.7%) were normoweight/underweight, 130 (31.1%) were overweight and 164 (39.2%) were obese. Another study reported that obese women have a 20% higher risk of developing TNBC compared with non-obese women (12). Taken collectively, these findings indicate that excess weight may be a factor significantly contributing to TNBC occurrence.

TNBC patients tend to have larger tumors, higher T stage and higher tumor grade. Results from previous studies demonstrated that obese TNBC patients tend to have larger tumors, higher T stage, and higher tumor grade. Ademuyiwa *et al* (11) reported that the mean tumor size in the overweight, obese and normoweight groups was 2.5, 2.3 and 2.2 cm, respectively. Another research from Louisiana (10) reported that the tumor size in obese, overweight and underweight/normoweight patients was 3.5, 3.3 and 2.3 cm, respectively, and that the overweight/obese patients had larger tumors (P=0.02), a higher T stage (P=0.001) and higher tumor grade (P=0.01) compared with the normoweight/underweight group. According to a research from China (13), where patients were classified based on tumor size, among patients with larger-sized tumors (>2 cm), 63.8% had a BMI >24 kg/m^2, and 58.3% had grade III tumors; among patients with tumors sized <2 cm, 6.2% had a BMI <24 kg/m^2, and 41.7% had grade I-II tumors.

Additional factors possibly associated with TNBC

Menopausal status. It was previously demonstrated that the risk of breast cancer in obese women was increased, but only in postmenopausal women. A prior Polish breast cancer study demonstrated that an increase in BMI decreased the risk of luminal A tumors in premenopausal women (14); however, the conclusions were based on analyses indicating that obesity exerts diverse effects on the risk of TNBC in pre-vs. postmenopausal women. A systematic review and meta-analysis evaluating the association among TNBC, obesity and menopausal status suggested that premenopausal women with BMI ≥30 kg/m^2 have a 42% higher risk of developing TNBC compared with non-obese women (12). It was concluded that menopausal status may be a factor mitigating the effect of obesity on the incidence of TNBC. A South American study drew similar conclusions, but this may be attributed to the higher incidence rates of TNBC observed among younger women of African American descent (15).

Diabetes. A positive association has been reported between overweight status and the incidence of type II diabetes in women (risk ratio=3.92; 95% CI: 3.10-4.97) (16). A multivariate analysis based on the medical database of 1,312 patients undergoing breast surgery demonstrated that diabetes was significantly associated with the triple-negative phenotype (OR=14.80, 95% CI: 1.92-113.91) (17). From this research, the high rates of TNBC have been primarily attributed to diabetes. Another study reported that insulin receptor (InsR) was highly expressed in ER- and PR-negative breast cancer cases (18). The potential association between diabetes and hormone receptor-negative breast cancer appears to be driven by higher InsR expression. However, the association between diabetes and TNBC has not been extensively investigated.

Waist-to-hip ratio (WHR). WHR, an index of the relative accumulation of abdominal vs. gluteal fat, is considered to be a significant indicator of obesity and a consistent factor associated with risk of breast cancer (19), regardless of menopausal status or parity, and may occasionally be a more stable measure compared with BMI. The Iowa Women's Health Study suggested that women with higher WHR had an increased risk of developing breast cancer, but only in populations with a family history of breast cancer. However, in the absence of a high WHR, a family history of breast cancer was not associated with a significantly increased cancer risk (20,21). An earlier study of a total of 172 TNBC cases observed that WHR was more significantly associated with the risk of TNBC compared with other subtypes (22). A prospective cohort study of 518 TNBC patients reported that WHR was higher among obese TNBC patients (23). The significant negative effects of increased WHR on the risk of basal-like breast cancer were observed among both pre- and postmenopausal women, except those with the luminal A subtype (22). Interestingly, the triple-negative phenotype was previously considered to behave clinically similar to the basal-like subtype (24,25). When the two parts of WHR were examined separately, increased waist circumference displayed a stronger positive association with breast cancer risk compared with hip circumference.

Use of hormonal therapy (HT). As HT is widely used among patients who eventually develop breast cancer, it has been hypothesized that HT use may increase breast cancer risk (26). Although women with TNBC were less likely to have received HT, overweight women who had never received HT were at a higher risk of developing TNBC compared with overweight women who had been treated with HT. A previous population-based case-control study reported that, among menopausal women without HT, BMI and weight were associated with the risk of TNBC (OR=2.7; 95% CI: 1.0-7.5 and OR=5.1; 95% CI: 1.1-23.0, respectively), and women in the highest weight quartile were at a 5.1-fold higher risk of TNBC (95% CI: 1.1-23.0; P=0.03), which was significantly higher compared with that of other breast cancer subtypes (27). However, neither BMI nor weight were found to be associated with the risk of TNBC among users of HT. Moreover, a stronger positive association between BMI and the risk of TNBC was observed in postmenopausal women who did not receive HT (27).

3. Biological rationale: Obesity and TNBC development

Significant progress is being made toward understanding the molecular mechanisms of TNBC, and the molecular basis of TNBC progression has been extensively investigated. A better

understanding of these mechanisms may help design a novel therapy for TNBC.

The role of estrogen in TNBC. There is evidence indicating that ovariectomy inhibits the development of ER-positive as well as ER-negative breast cancer (28). Conceivably, the effects of estrogen are likely to be underestimated in TNBC. The New England Journal of Medicine has reported that oophorectomy decreases the risk of breast cancer in women expressing breast cancer 1 (BRCA1) susceptibility protein (29). However, the vast majority of BRCA1 tumors are ER-negative. One possible explanation is that estrogens act independently of ER in the pathogenesis of ER-negative breast cancer. Subsequent studies in several reports demonstrated that an improvement of estrogen understanding and characterization challenges the long-held view that only ER-positive breast cancer is stimulated by estrogens. Gupta *et al* (30), from the Department of Biology, Massachusetts Institute of Technology, utilized a xenograft model to demonstrate that circulating estrogens are required for the formation of ER-negative tumors; furthermore, steroid hormones contribute to the outgrowth of ER-negative cancers via a systemic increase in host angiogenesis and the recruitment of bone marrow-derived stromal cells, both of which may be sufficient to promote TNBC growth.

Haplotypes of the 17h-hydroxysteroid dehydrogenase 1 gene (17HSD1). The 17HSD genes (EDH17B1 and EDH17B2) encode this enzyme that catalyzes the conversion of estrone to estradiol. EDH17B2 has been mapped to chromosome 17, region q12-q21, in the vicinity of the BRCA1 gene (31,32). Previous studies reported that germline BRCA1 mutations appear to be associated with TNBC (33-35). The 17HSD enzyme has been shown to be expressed in breast epithelial cells, it may affect the estrogen-dependent growth of breast epithelial cells (36) and, thus, it may play a role in the regulation of intracellular estrogen concentrations. The Breast and Prostate Cancer Cohort Consortium recently reported that two haplotypes of the 17HSD1 were more strongly associated with the risk of ER-negative, but not ER-positive, breast cancer (37). Among obese women (BMI >30 kg/m^2), the AA genotype of +1954A/G of HSD17B1 was associated with an increased risk of breast cancer (OR=1.77; 95% CI: 0.99-3.17) (37).

Insulin resistance, insulin-like growth factor 1 (IGF-1) and IGF-binding proteins (IGFBPs). A meta-analysis demonstrated that the overall breast cancer risk was significantly higher in the upper categories of C-peptide/insulin (38). IGF-1 exhibits a strong anti-apoptotic activity and exerts a significant effect on the control of cell and body size (39). In breast cancer specimens, studies have also demonstrated that the levels and activity of IGF-1 are increased compared with normal breast (40), and it has been proven by evidence from experimental studies that elevated levels of serum IGF-1 are correlated with increased breast cancer risk (41-45). All breast cancer subtypes express IGF receptors (46), although higher IGF-1R activity has been observed in TNBC cell lines (47). The accompanying evidence on high IGF-1R activity in TNBC cell lines indicates that IGF-1R may promote TNBC development, which is consistent with upward trends in the incidence of obesity among TNBC cases. Mutation of tumor suppressor genes, such as BRCA1 and p53, however, abrogate their inhibitory activity to increase the level of expression of the IGF-1R gene (48). IGFBP-3 is one of six proteins that bind IGF-I and -II with high affinity, and is correlated with markers of poor prognosis, such as ER and PR negativity, S-phase fraction and tumor size (49,50). IGFBP-3 was positively correlated with BMI (51) and TNBC was found to be associated with high expression of epidermal growth factor receptor (EGFR) and IGFBP-3 (52,53). IGFBP-3 contributes to the growth of TNBC cells by increasing SphK1-mediated EGFR signaling (54).

Leptin. Leptin is a cytokine discovered by positional cloning of the obesity gene (55). As body weight and fat mass increase, circulating levels of leptin increase as well. Leptin and leptin receptor (ObR) were significantly overexpressed in TNBC, and ObR expression was induced by hypoxia in TNBC cells (56). Obesity is associated with tissue hypoxia (57). Higher levels of circulating leptin promote breast cancer cell proliferation by activation of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3 kinase signaling pathways (58). IGF-1 induces ObR-b phosphorylation and leptin induces IGF-1R phosphorylation, whereas leptin and IGF-1 synergistically increase the activation of EGFR in breast cancer cells. The significant bidirectional crosstalk between leptin and IGF-I signaling augments TNBC cell migration and invasion potential (59).

Adiponectin. Adiponectin is the most abundant adipokine and is exclusively secreted by mature adipocytes (60). Adiponectin expression and serum levels are reduced in humans with obesity and insulin resistance (61,62). The serum adiponectin level was found to be inversely associated with the glucose level (63). High glucose levels may amplify the mitogenic and proliferative effects of leptin on mammary epithelial cells, and stimulate the proliferation of breast cancer cells (64). In addition, adiponectin directly inhibits the proliferation of vascular smooth muscle cells (65). Unexpectedly, these findings were observed in ER/PR-negative, rather than ER/PR-positive patients (66). Adiponectin levels within the physiological range significantly suppressed the proliferation of MDA-MB-231 cancer cells (67) and, concomitantly, adiponectin may promote the expression of Bax and p53, two pro-apoptotic genes (68). Decreased adiponectin levels are associated with increased risk of TNBC development in obese patients.

4. Treatment of TNBC

TNBC is more likely to exhibit an aggressive behavior and is associated with an unfavorable prognosis compared with other subtypes of breast cancer (6). TNBC often responds poorly to traditional chemotherapy. Thus, the development of novel targeted therapies for this aggressive type of breast cancer is of paramount importance.

Metformin. Metformin is the most frequently used treatment for diabetes. Metformin does not only increase insulin sensitivity, but also significantly reduces body weight. In addition, metformin was found to exert unique anti-TNBC effects *in vitro* as well as *in vivo* (69,70). The unique effects reported herein are metformin-induced apoptosis, proteolytic cleavage

of poly (ADP-ribose) polymerase, activation of caspase-3, -8 and -9, reduction of EGFR and P-EGFR (at both the auto- and Src activation sites), P-Src, P-MAPK and cyclin E, in a dose- and time-dependent manner.

Fenofibrate. Fenofibrate is a fibric acid derivative and plays an important role in reducing serum cholesterol and triglyceride levels, and increasing the levels of high-density lipoproteins (71). It has been demonstrated that fenofibrate induces TNBC cell apoptosis through the activation of the nuclear factor-κB pathway in a peroxisome proliferator-activated receptor-α-independent manner. Fenofibrate slowed down the growth of cancer cells in a xenograft model of TNBC by inducing apoptosis, with a good safety profile (72).

EGFR-targeting inhibitor. EGFR, also referred to as HER1, belongs to the HER family of transmembrane receptor tyrosine kinases, and plays important roles in the proliferation and metastasis of tumor cells (73-75). Dysregulation and the aberrant activation of EGFR induce uncontrolled tumor cell proliferation and invasiveness, decreased apoptosis and cell differentiation, and increased survival, angiogenesis, cell migration and metastasis (76,77). TNBC is associated with a high frequency of EGFR dysregulation (78,79), and EGFR expression is reported in >50% of TNBC cases. Activation of EGFR provides a potent survival signal in breast cancer, and this activation has been observed in response to a variety of stimulants, including IGF-1 (80) and leptin (81). Lapatinib and erlotinib successfully suppress invasion and migration of TNBC cells induced by combined therapy with leptin and IGF-1. It is reasonable to hypothesize that obese TNBC patients may optimally benefit from EGFR-targeted therapies (82,83).

ObR antagonists. The expression levels of leptin and ObR were found to be associated with distant metastasis of breast cancer (84), and ObR is an attractive target for the treatment of TNBC. It has been proven that both leptin and ObR were overexpressed in human TNBC tissues (92 and 86%, respectively). Allo-aca (the ObR antagonist peptide) prolonged the average survival time of mice with TNBC xenografts by 80% (85). These results suggest that Allo-aca has more advantages (superior efficiency, lower risk of gaining weight) compared with conventional treatment, and indicate that ObR antagonists may be a viable option for TNBC treatment, particularly in overweight patients.

Anti-IGF-1R/InsR therapy. TNBC progression is predominantly under IGF-1 control and, therefore, likely to be associated with the treatment of TNBC. Findings from TNBC cell studies led to a hypothesis that the inhibition of IGF-1R/InsR resulted in TNBC cell apoptosis. MC1 is the primary human tumorgraft of TNBC; treatment with a dual anti-IGF-1R/InsR inhibitor achieved growth inhibition and, combined with docetaxel, achieved complete tumor regression (47). Consistent with prior reports, anti-IGF-1R/InsR therapy in combination with chemotherapy is another attractive therapy option for patients with TNBC. In addition, IGF-1R/InsR therapy may moderate the effect of weight gain compared with EGFR-targeting inhibitors.

5. Prognosis of TNBC

It is widely hypothesized that obesity is associated with aggressive cancer behavior and an unfavorable prognosis (86). An analysis from International Breast Cancer Study Group trials indicated that BMI is an independent prognostic factor for OS in patients with breast cancer (87). Another study suggested that high BMI is associated with approximately a doubling of the mortality risk from breast cancer (88). Elevated body weight was associated with a significant increase in the risk of unfavorable prognosis of breast carcinoma in pre- and postmenopausal women (86,89). Similarly, it was demonstrated that, when adjusted for other factors, BMI exerts a significant effect on prognosis (87). Although a statistically significant association between obesity and recurrence or survival of breast cancer was demonstrated in some reports, others were unable to disentangle the effect of obesity from that of other potential factors, e.g., one study only investigated black and Caucasian women (90), whereas another only included women undergoing standard radical mastectomy, without other adjuvant therapy (91). However, several studies have directly pointed out that there is no association between obesity and survival or recurrence of breast cancer (92-94).

The abovementioned studies reported the association of obesity with survival, but did not explore the hormone receptor status (95). Although there is evidence linking body weight to outcome in breast cancer patients, the association between BMI and clinical survival in TNBC is less clear. It was previously demonstrated that obesity was not associated with decreased OS or disease-free survival (DFS) in patients with TNBC (10). The results of three adjuvant trials clearly established an association between higher BMI and higher risk of recurrence and death in luminal A breast cancer, but not in TNBC (96). Moreover, no significant association between obesity and recurrence-free survival or OS emerged in patients with TNBC after controlling for clinically significant factors (11). However, a Chinese report pointed out that high BMI was an independent prognostic factor for TNBC (97). A pooled analysis of eight prospective neoadjuvant breast cancer trials containing >8,800 patients demonstrated that increasing BMI results in decreasing pathological complete response (pCR) rates and that a high BMI exerts detrimental effects on DFS and OS in TNBC (98). Women with ER/PR-negative tumors exhibit a significant association of obesity with clinical outcome, which is also true for ER/PR-positive breast cancer (99). These contradictory findings cannot establish a clear association between the poorer outcome of TNBC and higher BMI.

6. Conclusions and prospects

The present review is one of the few to focus on the association between obesity and TNBC. Although there is a long-established correlation between the incidence of breast cancer and significant weight gain, the true association between obesity and TNBC does not appear to be clearly defined. Until recently, research on breast cancer has been more focused on the association between obesity and TNBC. A higher proportion of obese patients suffered from TNBC and the risk of TNBC was associated with an increase in BMI. While TNBC

patients tend to have higher BMIs compared with non-TNBC patients, there remain several unanswered questions, including whether this association holds for populations of different ethnic backgrounds.

Although there is a potential association between diabetes and obesity outcomes, there is limited information on how diabetes may affect the incidence of TNBC. Diametrically opposed incidence of TNBC was observed in pre- and post-menopausal cases. Anthropometric measures other than BMI, such as waist-to-hip ratio, may be better measures of adiposity in terms of TNBC risk. The apparent positive association of obesity with the risk of TNBC was incrementally attenuated with hormone therapy.

Obesity profoundly alters the development of TNBC, but the mechanisms that link obesity and TNBC risk have not been fully elucidated. It has been hypothesized that the effect of estrogen on breast cancer development may differ between women with ER-positive tumors and those with ER-negative tumors, and the potential biological mechanisms include increased levels of endogenous factors (sex steroids, haplotypes of the 17HSD1, leptin, adiponectin, insulin and IGFI) associated with the contribution of overweight status or abdominal obesity to TNBC.

As TNBC patients are unresponsive to current targeted therapies and other treatment options are only partially effective, new pharmacological therapies are urgently needed. Against this background, novel treatment of this aggressive type of breast cancer is a field that has recently attracted increasing attention. The advent of therapies based on mechanisms that target critical molecular pathways of cancer has evoked considerable interest. Novel treatments, such as metformin, fenofibrate, EGFR-targeting inhibitors, ObR antagonists and anti-IGF-IR/InsR therapy, are currently considered as excellent targets for TNBC chemotherapy. With these advances comes a potential for improved therapeutic strategies that may lead to a favorable prognosis, but the results must be interpreted with caution and they require further validation in animal models and human clinical studies, coupled with pathology research investigating molecular correlates of a possible effective response; such research is currently underway in several institutions.

Findings from animal and human studies led to the hypothesis that obesity leads to aggressive cancer behavior and contributes to worse outcome. It was initially hypothesized that obesity may contribute to poorer breast cancer outcome. In addition, the negative effects of higher body weight on breast cancer recurrence and survival are observed in both pre- and postmenopausal women. Therefore, BMI exerts a significant effect on prognosis, even when adjusted for other factors. Although previous studies have consistently demonstrated associations between adiposity and poor prognosis of breast cancer, hormone receptor status was not discussed in terms of outcome. Consequently, data on TNBC are scarce or inconsistent. More recent research has indicated that high BMI adversely affected DFS and OS, independently of pCR, in TNBC, and it exerted a detrimental effect on survival in TNBC. However, International Breast Cancer Study Group trials between 1978 and 1993 have demonstrated that lack of sufficient proof led to the emerging concept that obesity cannot be a prognostic factor for TNBC (100). The lack of consistency may be attributable to the limited number of studies. It is also likely that the stronger associations observed in the present review reflect a greater effect of BMI on the incidence rather than on the mortality of TNBC. In the present review, we were unable to demonstrate that the high rate of deaths from TNBC is attributable to overweight status and obesity.

Breast cancer is a major health concern worldwide. Some efforts have been made to create an integrated measure of TNBC. Obesity and reduced physical activity have been found to contribute to the increasing trend in the incidence of TNBC. Considering the pathophysiological behavior of obesity-related genes, such as leptin, adiponectin, insulin and IGF-I, a combination of lifestyle changes, including dietary habits, and different drug regimens, may be useful in intercepting the disease course of obesity-related breast cancer. Therefore, maintaining an optimal body weight is a valuable preventive measure for TNBC.

To provide insights into the complex associations of this disease, future analyses of body size and breast cancer should investigate potential interactions between receptor status and body size, in order to elucidate the precise association between obesity and TNBC, and draw more attention to the role of primary prevention, early diagnosis and treatment.

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