Editorial

Metformin: a potentially winning therapeutic strategy to prevent breast cancer progression in overweight postmenopausal patients

Danila Coradini

Laboratory of Medical Statistics and Epidemiology, 'Giulio A. Maccacaro', Department of Clinical Sciences and Community Health, University of Milan, Milan 20133, Italy

Correspondence to: Danila Coradini. Laboratory of Medical Statistics and Epidemiology, 'Giulio A. Maccacaro', Department of Clinical Sciences and Community Health, University of Milan, Via Vanzetti 5, Milan 20133, Italy. Email: danila.coradini@gmail.com.

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Growing body of literature supports the evidence that, in postmenopausal women, breast cancer initiation and progression are close associated with a series of interconnected factors which include weight gain, metabolic syndrome and increase of circulating androgens. For that reason, there is mounting interest in identifying novel therapeutic approaches able to contrast the detrimental effects of these factors, thereby reducing breast cancer risk and improving outcome in women with established tumor. Accumulating evidence suggests that metformin, an antidiabetic drug widely used for its low toxicity profile and low cost, could represent a potentially winning approach also for the treatment of breast cancer. In this perspective, a study recently published by Giles *et al.* (1)—aimed to investigate the impact of metformin on the expression of stromal aromatase in an animal model of postmenopausal breast cancer—has provided interesting information on the indirect mechanisms that allow achieving the antitumor effect. However, to better understand the biological bases for using metformin as an adjuvant agent, is essential to recall the complex interrelation among weight gain that follows loss of ovarian function after menopause, increase of circulating levels of androgens—especially testosterone—and androgens conversion into estrogens occurring in adipose tissue via aromatase enzyme.

With the decline of the ovarian function and consequent falling in estrogens production, testosterone promotes the redistribution of body fat that preferentially accumulates in the abdomen (2). This excess of visceral fat—known as central obesity—plays a relevant role in favoring the onset of insulin resistance and the associated hyperinsulinemia which, in turn, stimulate the ovarian synthesis of androgens and concomitantly inhibit the hepatic production of sex hormone-binding globulin (SHBG), the carrier protein that binds and sequesters free testosterone, preventing its conversion into estradiol by aromatase enzyme (3). Since serum concentration of SHBG is the final result of the stimulatory action of estrogens and the inhibitory action of androgens and insulin, the physiological decline of estradiol concentration after menopause, in addition to the concomitant reduction of SHBG production in the liver due to hyperinsulinemia, determines a marked decrease of circulating levels of SHBG. Consequence of this reduction is the increase of free testosterone levels that, in turn, enhance insulin resistance by promoting visceral fat accumulation, therefore triggering a dangerous vicious circle (4).

The main peripheral source of aromatase is the white adipose tissue. Therefore, the abnormal accumulation of fat, besides an increased production of pro-inflammatory molecules that trigger and maintain low-grade inflammation (5), induces the continuous production of estradiol by androgens aromatization (6), providing the suitable milieu for the initiation and progression of breast cancer by promoting and sustaining the proliferation of cells expressing estrogen receptor (ER) (7). It has been evaluated that the concentration of estradiol in breast tumors of postmenopausal women is at least 20-fold greater

than plasma concentration (8).

In accord, epidemiologic and clinical studies have shown that, especially in postmenopausal women, the increase of body fat, evaluated as body mass index (BMI), is associated with the occurrence and progression of ER-positive breast cancer (9,10). However, very recent findings indicated that the relationship among BMI, circulating androgens and risk of relapse is more complex than expected, with a different impact of circulating testosterone on the risk of relapse, depending on BMI categories (11). In fact, in normal-weight patients, the risk of relapse showed a bell-shape course with increasing risk of relapse for intermediate levels of testosterone and low risk of relapse for low and high levels of testosterone, whereas, in overweight patients, the risk of relapse increased with increasing testosterone levels in a linear manner. Surprisingly, obese patients showed an inverse relationship between testosterone levels and risk of relapse; in other words, high levels of testosterone were associated with a low risk of relapse. Because in obese patients, breast tumors are more frequently androgen receptor (AR)-positive than in normal-/overweight women, a possible explanation for the unexpected protective effect of high levels of testosterone, is the activation of the AR-dependent axis rather than the ER-dependent one. In fact, according to the metabolic pathway followed, testosterone can act either as proliferation promoter or inhibitor. When converted to estrogen by the tissue aromatase, testosterone exerts a stimulatory effect via ER (12), whereas when converted to dihydrotestosterone (DHT) by 5α-reductase, it binds to AR, abrogates ER-mediated signaling and induces the expression of genes involved in the inhibition of cell growth (13). Clinical evidence corroborates this hypothesis and indicates that AR overexpression, high levels of DHT or a low aromatase/5α-reductase ratio are associated with a better prognosis (14,15). An additional explanation for the unexpected protective effect of high levels of testosterone in obese patients is provided by a recent study aimed to investigate the prognostic impact of circulating levels of testosterone and SHBG (16). Obese patients with high levels of both total testosterone and SHBG—i.e., with a low testosterone/SHBG ratio which corresponds to low levels of free (and therefore available) testosterone—showed a longer disease-free survival than obese patients with high levels of testosterone but low levels of SHBG, i.e., with a high testosterone/SHBG ratio.

Given this complex scenario, it is evident that classic tumor-associated markers including tumor size, axillary lymph nodes status, steroid receptors and HER-2 status, and proliferative activity are no more sufficient to evaluate prognosis and establish the suitable therapy for the treatment of postmenopausal breast cancer patients. The inclusion of some patient-associated features such as BMI and circulating levels of testosterone and SHBG, could improve the decision-making process addressing the therapeutic strategy towards the use of drugs able to neutralize, at least in part, the detrimental effect of metabolic dysfunctions such as insulin-resistance and obesity.

The recent study from Giles *et al.* (1) about the inhibitory activity of metformin on the expression of stromal aromatase provides new interesting insights on the potential use of this drug as adjuvant treatment of ER-positive breast cancer in postmenopausal patients. In fact, despite the limitations related to the use of animal models, results indicated that, besides to decrease pre-existing tumor mass and prevent the formation of new tumors in both normal-weight and obese animals submitted to ovariectomy to simulate menopause, metformin inhibited the expression of stroma-derived aromatase by decreasing the number of a subpopulation of protumorigenic, M2-like macrophages (CD68+), present in high amount in inflamed mammary adipose tissue and characterized by the expression of aromatase enzyme.

As known, macrophages can exhibit pro- or antitumor activity according to their polarization state. While pro-inflammatory macrophages (M1 phenotype) are considered tumor suppressive because involved in immune surveillance, antigen presentation, and killing of cells with unknown antigens including tumor cells, anti-inflammatory macrophages (M2 phenotype) are considered immunosuppressive and can promote tumor progression (17,18). Aromatase-positive CD68+ macrophages, which accumulate in the mammary adipose tissue of overweight and obese animals, exhibit a M2-like phenotype.

According to authors' conclusions, in addition to the direct effects on tumor cells, metformin seems to be able to decrease the local production of estrogens by reducing the number of aromatase-positive macrophages and preventing the conversion of androgens into estrogens.

Several studies have explored and described the causal link among obesity, adipokines-induced low-grade inflammation, and local production of estrogens in breast cancer (19,20), and some have specifically investigated the macrophage production of aromatase (21).

On the whole, these studies have demonstrated that obesity is characterized by the accumulation of distinct

populations of macrophages predominantly at sites known as crown-like structures (CLS) around dead adipocytes. Among these subpopulations, CLS-associated CD9+ adipose tissue macrophages (ATMs) are the predominant ATM group responsible for the inflammatory signature of obese adipose tissue, whereas CD68+ ATMs are characterized by the expression of aromatase enzyme (22,23). Positively correlated with BMI (24), aromatase-positive CD68+ ATMs add their aromatase activity to that of pre-adipocytes stimulated by pro-inflammatory modulators, therefore increasing the local production of estrogens which fuel transformed cells proliferation.

Within this context, the capability of metformin to reduce the number of aromatase-positive ATMs, and therefore the amount of locally available estrogens in overweight/obese postmenopausal women with established breast cancer appears rather attractive, especially considering the low toxicity and the low price, which allow a safe and economically sustainable log-term treatment. In particular, considering the protective role played by the low testosterone/SHBG ratio and/or the increased expression of AR in obese patients, metformin is expected to be more effective in overweight patients in which, despite the moderate increase of adiposity, the presence of high circulating levels of free testosterone and the concomitant increased aromatase activity of pre-adipocytes and aromatase-positive ATMs, allows the local production of estrogens, which in turn stimulate and sustain tumor cells proliferation.

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