Redox profile of breast tumor and associated adipose tissue in premenopausal women - Interplay between obesity and malignancy

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ABSTRACT

One of the underlying mechanisms that could link breast cancer and obesity is shifted redox homeostasis in the tumor microenvironment. To reveal the relationship between the malignant phenotype and obesity, we compared redox profiles of breast tumor and tumor-associated adipose tissue from premenopausal women: normal-weight with benign tumors, overweight/obese with benign tumors, normal-weight with malignant tumors, and overweight/obese with malignant tumors. Namely, we examined the protein expression of nuclear factor erythroid 2-related factor 2 (Nrf2), protein expression and activity of main antioxidant defense (AD) enzymes: copper, zinc- and manganese superoxide dismutase, catalase, and glutathione peroxidase, as well as the level of 4-hydroxy-2-nonenal (4-HNE) modified proteins. Higher protein expression and activity of AD enzymes were found in malignant tumor tissue than benign tumor tissue, irrespective of obesity. Nevertheless, malignant tumor tissue of overweight/obese women was characterized by higher protein expression of Nrf2 and weaker immunopositivity for 4-HNE modified proteins. In malignant tumor-associated adipose tissue, the redox profile was clearly related to obesity. Higher Nrf2 protein expression and higher AD enzyme levels were observed in normal-weight women, while stronger immunopositivity for 4-HNE modified proteins was found in overweight/obese women. The results suggest that the complex interplay between obesity and malignancy involves redox-sensitive pathways in breast tumor and tumor-associated adipose tissue.

1. Introduction

Breast cancer is the most prevalent malignancy in women, with the highest mortality rate worldwide. Excess body weight is a known risk factor for breast cancer in postmenopausal women, contributing to more severe disease progression [1–3]. However, evidence linking obesity to breast cancer in premenopausal women remains inconclusive [4–7].

One of the underlying mechanisms that could link obesity and breast cancer is shifted redox homeostasis in breast tissues. Since the pioneering work of Warburg and Oberley, metabolic reprogramming and underlying changes in redox regulation have been recognized as hallmarks of neoplastic transformation [8]. The chief characteristics of cancer cells are mediated by redox-sensitive cellular processes that serve to sustain the malignant phenotype, i.e., genomic instability, proliferation, migration, and apoptosis [9]. Accordingly, malignant cells are often characterized by atypical redox signaling, different reactive species generation rates, and altered levels of antioxidant defense (AD) enzymes. This is evident as increased production of reactive oxygen species (ROS), presence of oxidative stress biomarkers (e.g., 8-hydroxy-2′-deoxyguanosine, protein carbonyls, 4-hydroxy-2-nonenal protein adducts, malondialdehyde), as well as tumor-specific overexpression or underexpression of several redox proteins [10–12]. A delicate balance between ROS production and neutralization could reflect the metabolic blueprint of every cancer, determining its invasiveness, metastatic potential, and resistance to conventional therapies. It is recognized that obesity, as a chronic state of altered energy homeostasis, can affect the metabolism of different tissues, including cancer [13,14]. Our recent study showed obesity-related changes to the lactate metabolism in the breast cancer microenvironment [15]; however, the impact of obesity on cancer tissue redox homeostasis has not been studied thoroughly.

On the local level, dysfunction of resident adipose tissue in obesity may be one of the critical features that contribute to cancer initiation and progression. Fat accumulation leads to systemic and adipose tissue (AT) localized prooxidant state [16], mainly attributed to stimulated ROS generation and decreased activity of superoxide dismutase (SOD) isoforms [17]. Moreover, adipose tissue possesses unique morpho-functional plasticity that comes to light in obesity. Adipogenesis, adipose hypertrophy, and hyperplasia are supported by redox-driven alterations in glucose homeostasis, oxidative metabolism, and antioxidant defense [18]. Such processes of local tissue remodeling are potentially responsible for establishing and sustaining the tumor microenvironment. The relationship between malignancy and obesity deepens by our increasing understanding of the importance of cancer-adipose tissue cross-talk. This complex communication, recently termed *adipocyte cancer cell paracrine loop*, leads to excessive mutual remodeling and promotes overall cancer aggressiveness [19–22]. However, cancer-adipose tissue cross-talk is mostly studied *in vitro*, in the light of paracrine functions of growth factors, adipokines, and proinflammatory cytokines. Human studies considering the morpho-functional specificity of the mammary adipose depot, especially in complex physiological states such as obesity, are still scarce [17,23, 24].

This study aimed to reveal the redox profile related to the malignant phenotype and its relationship with obesity in premenopausal women. To this end, we examined the protein expression of transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), the activity and protein expression of first-line AD enzymes: copper, zinc- and manganese superoxide dismutase (CuZnSOD and MnSOD, respectively), catalase (CAT), glutathione peroxidase (GSH-Px) and level of 4-hydroxy-2-nonenal (4-HNE) modified proteins in paired biopsies of tumor tissue and associated adipose tissue from normal-weight and overweight/obese women with breast cancer. As respective controls, paired biopsies of tumor tissue and associated adipose tissue from normal-weight and overweight/obese women with non-malignant (benign) breast changes were used.

2. Materials and methods

2.1. Subjects and sample collection

This study followed the standards set by the latest version of the Declaration of Helsinki. The ethics committee of the Clinical Center of Vojvodina approved all the procedures. Patients volunteered for the study and signed an informed consent form. The study group consisted of 36 women who were hospitalized for breast surgery. All subjects were premenopausal (with regular menses for the last six months) with an average age of 39.8 ± 8.77 years. Indications for surgical intervention were benign cases of breast fibroadenoma or malignant cases of luminal type A ($ER^+/PR^+/HER2^-$) invasive ductal carcinoma. At the beginning of the surgical procedure under general balanced anesthesia, samples of breast tumor and tumor-associated adipose tissue (in the immediate vicinity to the tumor mass) were obtained. From each patient, one piece of the tumor and the adipose tissue sample was snap-frozen in liquid nitrogen and stored at $-80\ °C$ until subsequent protein isolation by TRI Regent procedure (Ambion, USA) for protein expression analysis by Western blot. The remaining piece was homogenized (Heidolph DIAX 600) at $0–4\ °C$ in 0.25 M sucrose, 0.1 mM EDTA, and 50 mM Tris buffer, pH 7.4 for enzyme activity measurements. Body mass index (BMI) was used to classify samples as normal-weight (BMI < 25 kg/m^2) or overweight/obese (BMI ≥ 25 kg/m^2) [25]. According to the tumor type and BMI, samples were further classified into four groups (n = 9); normal-weight (non-obese) with benign tumors, overweight/obese with benign tumors, normal-weight (non-obese) with malignant tumors, and overweight/obese with malignant tumors.

2.2. Western blot analysis

Western blot analysis was conducted as described previously [26] using antibodies against: CuZnSOD (0.2 µg ml^{-1}; ab13498), MnSOD (0.2 µg ml^{-1}, ab13533), CAT (1 µg ml^{-1}; ab1877), GSH-Px (1 µg ml^{-1}; ab17926-500), Nrf2 (1 µg ml^{-1}; ab31163), 4-HNE (1 µg ml^{-1}; ab46545) and β-actin (0.5 µg ml^{-1}; ab8226) (all purchased from Abcam, Cambridge, UK). Quantitative analysis of immunoreactive bands was performed with ImageJ software (National Institute of Health, USA). Total band density was calculated as the sum of pixel intensities within a band. The ratio of dots per band for the target protein was averaged against β-actin (gel loading control) from three independent experiments, and the levels of protein expression were expressed in arbitrary units (AU).

2.3. Immunofluorescence analysis

Standard immunolabeling procedure we conducted as previously described [27] using primary antibodies against 4-HNE (5 µg ml^{-1}; ab46545, Abcam, UK) and with the appropriate fluorochrome-conjugated secondary antibody (1:400; Alexa Fluor® 633 goat anti-rabbit, A2070, Thermo Fisher Scientific, USA). For counterstaining of the nuclei, Sytox Orange (1 µL ml^{-1}, Thermo Fisher Scientific) was used. Slides were mounted with Mowiol (Polysciences, Eppelheim, Germany), and confocal images were acquired with a Leica TCS SP5 confocal laser scanning microscope (Leica Microsystems, Austria) in sequential mode to avoid cross-talk between channels. The specificity of immunofluorescence was tested by the omission of primary antibodies. Image processing and quantification were performed with NIH Image J software.

2.4. AD enzyme activity

The activity of superoxide dismutase isoforms was determined using the method of Misra and Fridovich [28] and expressed in U mg^{-1} protein. Catalase activity was assayed according to the method of Beutler, and the activity was expressed in U mg^{-1} protein [29]. Glutathione peroxidase was determined using the method of Paglia and Valentine [30], and the activity was expressed in nmol of reduced NADPH min^{-1} mg^{-1} protein.

2.5. Statistics

Statistical analysis was performed in GraphPad Prism software (GraphPad Prism, Version 6.01). Normality of distribution for all data sets was assessed with D'Agostino and Pearson's omnibus normality test. One-way two-tailed analysis of variance (ANOVA) was applied for within-group comparison of the data from molecular analysis. If the F test showed an overall difference, multiple comparison Tukey's post hoc test was used to evaluate the significance of the among group differences. Statistical significance was accepted at $p < .05$.

3. Results

Protein expression of AD enzymes, Nrf2, and level of 4-HNE modified proteins in benign and malignant tumor tissue of normal-weight and overweight/obese women.

In general, malignant tumor tissue of normal weight and overweight/obese women displays increased protein expression of AD enzymes in comparison to benign tumor tissue of weight-matched women. Namely, a clear difference in protein expression of CuZnSOD, CAT and GSH-Px was observed (CuZnSOD (normal-weight) $p < .05$, CuZnSOD (obese) $p < .01$; CAT(normal-weight) $p < .001$, CAT(obese) < 0.001; GSH-Px (normal-weight) $p < .001$, GSH-Px (obese) < 0.001). Besides, there were no differences in protein expression of CuZnSOD, CAT, and GSH-Px between normal-weight and overweight/obese pairs of benign and malignant tumors. Higher protein expression of MnSOD was found

only in malignant tumor tissue of normal-weight women (p < .01). Interestingly, Nrf2 showed higher protein expression in malignant tumor tissue of overweight/obese women, compared to both its corresponding benign counterpart (p < .001) and to the malignant tumor tissue of normal-weight women (p < .01) (Fig. 1A–E). Semi-quantitative analysis of 4-HNE immunofluorescence intensity showed no significant differences between analyzed groups. However, Western blot analyses showed multiple prominent immunopositive bands for 4-HNE, where a weaker positivity corresponding to the 95 kDa band was found in malignant tumor tissue of overweight/obese women compared to their overweight/obese benign counterparts and malignant tumor tissue of normal-weight women (Figs. 1F and 5).

AD enzyme activity in benign and malignant tumor tissue of normal-weight and overweight/obese women.

There were no significant differences in CuZnSOD and MnSOD activity in the tumor tissue when weight-matched benign and malignant counterparts were compared, except for slightly higher CuZnSOD activity (p < .05) in overweight/obese women with malignant tumors. Clearly higher GSH-Px activity characterized malignant tumor tissue of both normal-weight (p < .01) and overweight/obese women (p < .05), compared to benign weight-matched counterparts. Similarly, a trend towards the higher activity of CAT was present in malignant tumor tissue in comparison to benign, irrespective of the BMI (Fig. 2).

Protein expression of AD enzymes, Nrf2, and level of 4-HNE modified proteins in tumor-associated adipose tissue of normal-weight and overweight/obese women with benign and malignant breast tumors.

Expression patterns of AD enzymes in tumor-associated adipose tissue were mainly consistent. Significantly higher protein expression of CuZnSOD, MnSOD, and CAT was found in adipose tissue of normal-weight women with malignant tumors, as compared to weight-matched women with benign breast tumors (p < .001) and to overweight/obese women with malignant tumors (p < .001). Higher protein expression of GSH-Px was found in tumor-associated adipose tissue of women with malignant tumors (p < .05), compared to their benign counterparts, regardless of BMI. In addition, protein expression of Nrf2 was found to be higher in adipose tissue of normal-weight women with malignant breast tumors, in comparison to weight-matched women with

benign tumors (p < .001) and overweight/obese women with malignant tumors (p < .01) (Fig. 3A–E). Semi-quantitative analysis of 4-HNE immunofluorescence intensity showed the strongest immunopositivity for 4-HNE modified proteins in adipose tissue of overweight/obese women with malignant tumors. Interestingly, Western blot analysis showed that the intensity of immunoreactive bands for 4-HNE at 40 kDa was higher in adipose tissue of overweight/obese women with benign tumors as well as in adipose tissue of normal-weight women with malignant tumors compared to adipose tissue of normal-weight women with benign tumors. However, additional immunoreactive bands for 4-HNE at 25 kDa were markedly visible only in adipose tissue of overweight/obese women with malignant tumors (Figs. 3F and 5).

AD enzyme activity in tumor-associated adipose tissue of normal-weight and overweight/obese women with benign and malignant breast tumors.

There were no differences in adipose tissue CuZnSOD and MnSOD activity between examined groups of women. Higher CAT and GSH-Px activity in adipose tissue of normal-weight (p < .05) and overweight/obese (p < .05) women with malignant tumors was observed, in comparison to respective adipose tissue of women with benign tumors (Fig. 4).

4. Discussion

This study evaluated the redox profile of breast tumor tissue and tumor-associated adipose tissue and its relationship with malignancy and obesity in premenopausal women. Cross-examination of malignant tumor tissue biopsies revealed higher protein expression and activity of investigated AD enzymes regardless of BMI compared to benign tumor tissue. Nevertheless, protein expression of Nrf2 in malignancy was associated with obesity. Interestingly, the redox profile of malignant tumor-associated adipose tissue was clearly BMI-related. Significantly higher protein expression of AD enzymes was found in normal-weight women, where activation of the Nrf2 pathway seems to play a role in establishing such "activated" phenotype in cancer-associated adipose tissue. The results suggest a specific redox-sensitive relationship between neoplastic transformation, mammary adipose tissue, and obesity
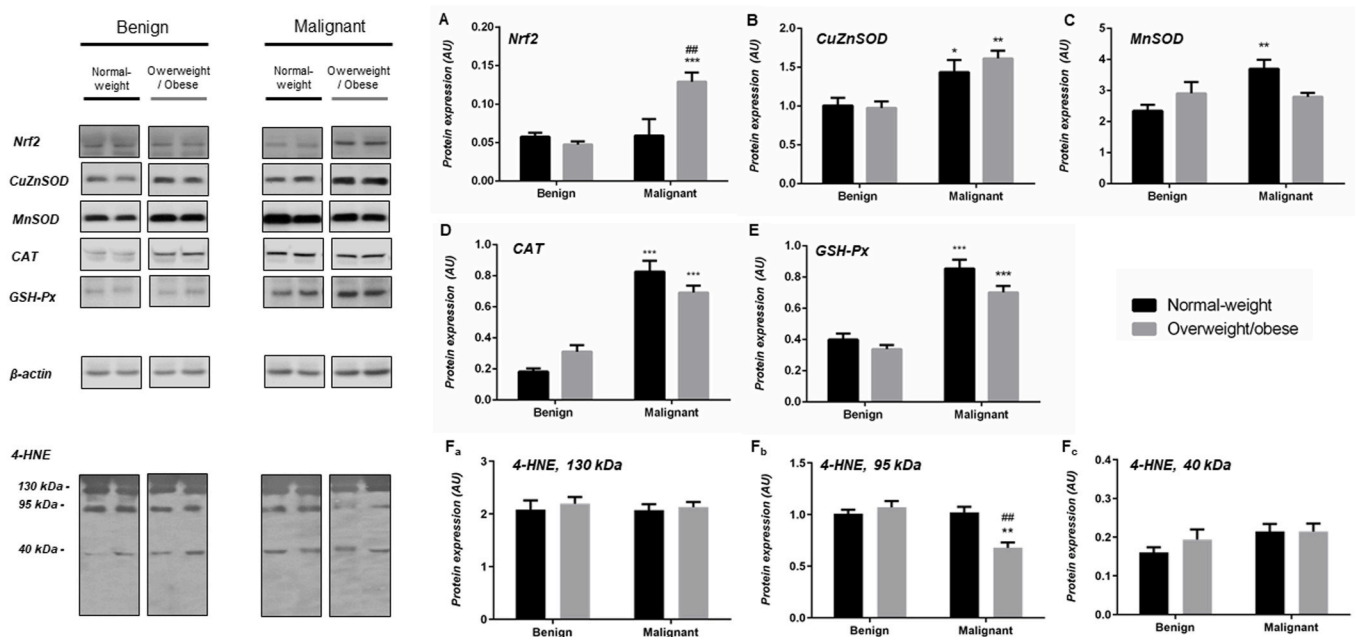
Fig. 1. Protein expression of Nrf2 (A), AD enzymes (CuZnSOD (B), MnSOD (C), CAT (D), GSH-Px (E)), and level of 4-HNE modified proteins (130 kDa (Fa), 95 kDa (Fb), 40 kDa (Fc)) in benign and malignant breast tumor tissue of normal-weight (black) and overweight/obese (gray) women. The protein content is expressed in arbitrary units (AU). Band images from a representative blot of three trials are shown. Bars represent the mean ± S.E.M. *Compared to respective benign counterpart, *p < .05, **p < .01, ***p < .001; # compared to normal-weight malignant counterpart, ##p < .01.
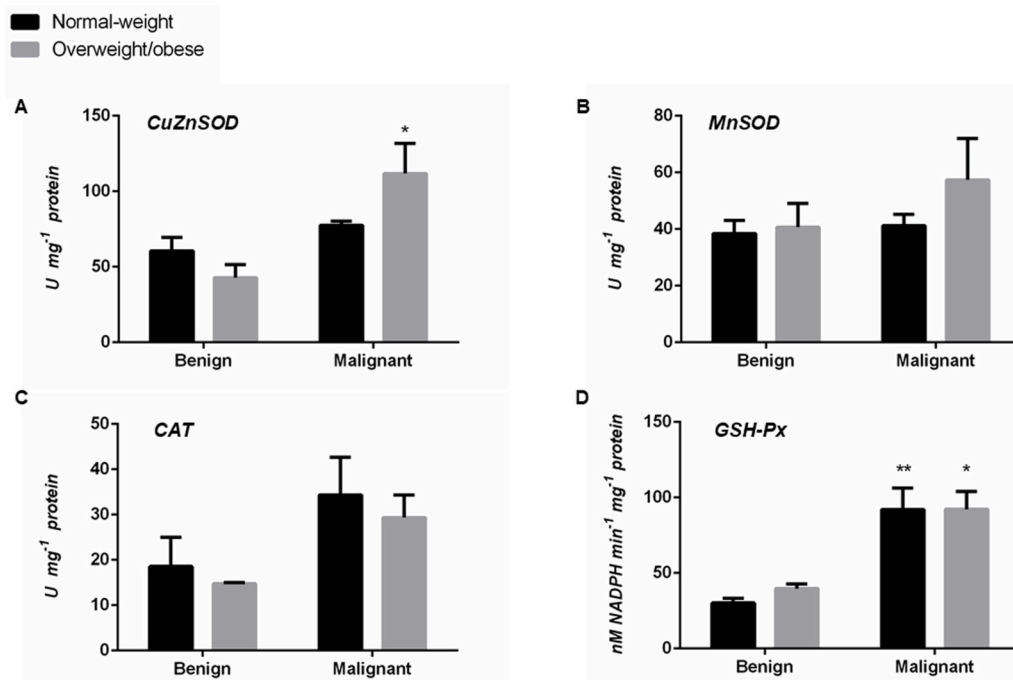
Fig. 2. The activity of CuZnSOD (A), MnSOD (B), CAT (C), and GSH-Px (D) in benign and malignant breast tumor tissue of normal-weight (black) and overweight/obese (gray) women. Enzyme activity is expressed in absolute units in U mg^{-1} protein (A, B, C) and nM NADPH min^{-1}mg^{-1} protein (D). Bars represent the mean ± S.E.M. *Compared to respective benign counterpart, *p < .05, **p < .01.
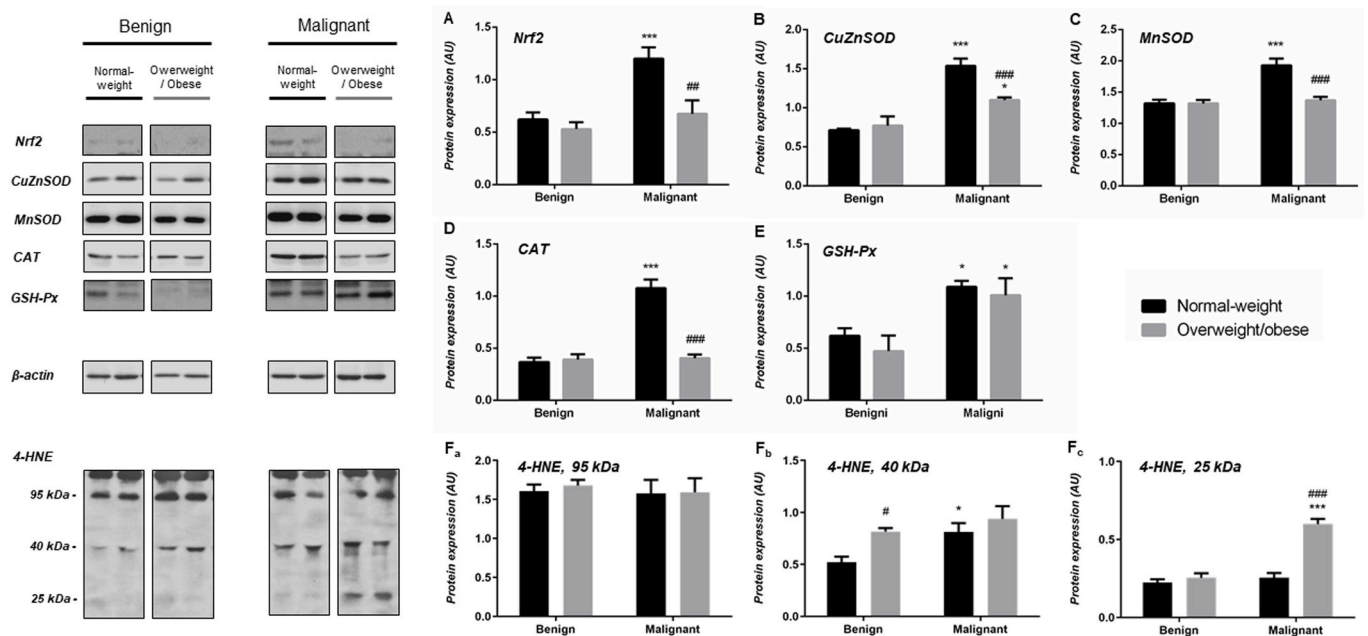

Fig. 3. Protein expression of Nrf2 (A), AD enzymes (CuZnSOD (B), MnSOD (C), CAT (D), GSH-Px (E)), and level of 4-HNE modified proteins (95 kDa (Fa), 40 kDa (Fb), 25 kDa (Fc)) in tumor-associated adipose tissue of normal-weight (black) and overweight/obese (gray) women with benign and malignant breast tumors. The protein content is expressed in arbitrary units (AU). Band images from a representative blot of three trials are shown. Bars represent the mean ± S.E.M. *Compared to respective benign counterpart, *p < .05, ***p < .001; # compared to normal-weight malignant counterpart, #p < .05, ##p < .01, ###p < .001.

in premenopausal women.

Redox profile represents a blueprint of every cancer, reflecting the stage of progression [31,32], metabolic demands [33,34], or selective pressures imposed by the tumor microenvironment [8,35,36]. Accordingly, data obtained for different types of tumors and at different stages of tumor progression *in vitro* and *in vivo* are inconsistent. Increased or decreased levels of ROS, oxidative stress biomarkers, and redox-related

proteins were associated with the malignant phenotype [37–50]. Furthermore, a shift towards oxidative or peroxidative state, evident as the relative disproportion in the expression of O2$^{•-}$ and H$_2$O$_2$ eliminating enzymes, has been previously described [51–53]. We show higher CuZnSOD, MnSOD, CAT, and GSH-Px protein expression and CAT and GSH-Px activity in malignant tumor tissue than in benign tumor tissue, irrespective of BMI. This is in agreement with the higher redox
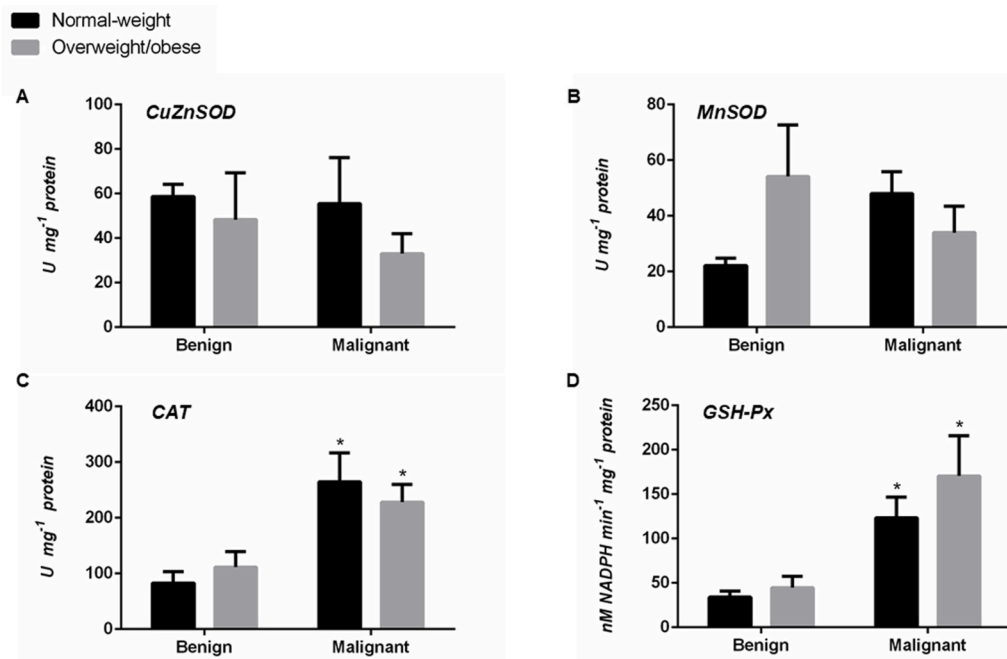
Fig. 4. The activity of CuZnSOD (A), MnSOD (B), CAT (C), and GSH-Px (D) in tumor-associated adipose tissue of normal-weight (black) and overweight/obese (gray) women with benign and malignant breast tumors. Enzyme activity is expressed in absolute units in U mg^{-1} protein (A, B, C) and nM NADPH min^{-1}mg^{-1} protein (D). Bars represent the mean ± S.E.M. *Compared to respective benign counterpart, *p < .05, **p < .01.
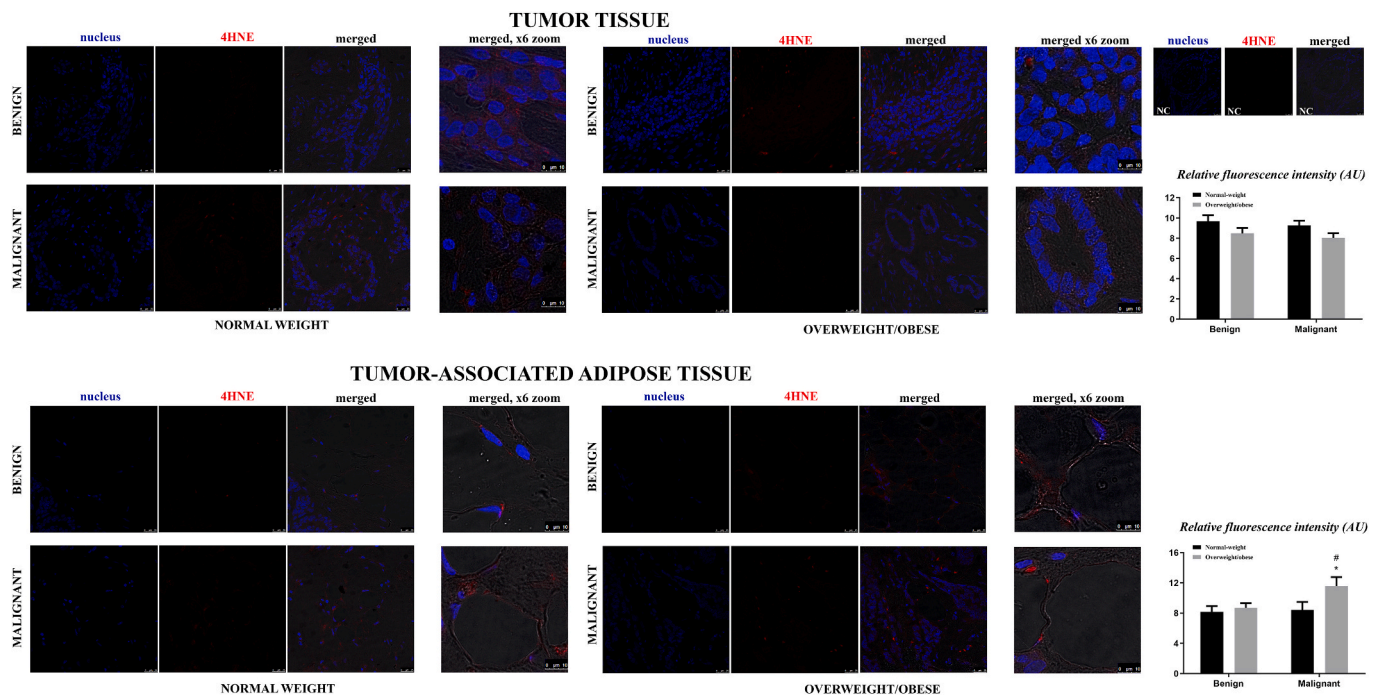
Fig. 5. Immunofluorescence staining and confocal microscopy of 4-HNE modified proteins presence and localization in breast tumor tissue and tumor-associated adipose tissue of normal-weight (black bars) and overweight/obese (gray bars) women with benign and malignant breast tumors. 4-HNE- (red) and nuclei Sytox Orange staining (false blue). Merged images are an overlay of two channels on phase-contrast tissue images. NC-negative control. Scale bars: 25 μm and 10 μm on merged x6 zoom.

homeostasis threshold hypothesis [54,55] and indicates a well-balanced capacity of malignant tumor tissue to metabolize ROS [44,52]. In an indirect assessment of ROS levels and lipid peroxidation rate, stronger immunopositivity for 4-HNE modified proteins was found in normal-weight women than in overweight/obese. In contrast, protein expression of transcription factor Nrf2 was higher in overweight/obese women with malignant tumors. Consistent with overall metabolic changes caused by systemic effects of obesity, cancer tissue metabolism has been previously shown to differ between normal-weight and overweight/obese women [15,56]. Differential protein expression of Nrf2 and level of 4-HNE modified proteins could reflect such obesity-related intricate metabolic differences, especially in the light of new evidence

for the pleiotropic role of Nrf2 in metabolic reprogramming [57–60] and a complex signaling role of 4-HNE in cancer [61–64]. Moreover, there is evidence to support a worse prognosis, shorter disease-free interval, and higher mortality in breast cancer patients with high Nrf2 expression [59, 65].

Local interaction between adipose tissue and cancer tissue has been recently shown to play an important role in cancer development and progression [20,22,66]. Cancer cells have been shown to communicate with adipocytes and "activate" their phenotype towards dedifferentiation, deregulated secretory activity, increased lipolysis, and β-oxidation [67]. In turn, adipocytes secrete free fatty acids, adipokines, proinflammatory cytokines, proteases, and components of the extracellular matrix to promote cancer invasion. It has been proposed that obesity could enhance two-way communication between these tissues [21, 68–71]. However, this has mostly been addressed in cell culture and co-culture studies, not fully considering the morpho-functional diversity of adipose tissue depots. Here, our data on paired human biopsies indicate that described cross-talk also affects redox-sensitive pathways _in vivo_. Initial assessment of adipose tissue from women with benign breast changes showed no significant obesity-related differences in Nrf2 and AD enzyme expression. However, cross-examination of malignant tumor-associated adipose tissue revealed a clear association between the redox profile and BMI. Higher protein expression of AD enzymes (CuZnSOD, MnSOD, and CAT) was found in normal-weight women, compared to overweight/obese. This could be related to the increased metabolic demands of cancer tissue, which favor oxidative metabolism [22,72]. Indeed, AD enzyme levels in adipose tissue were parallel to those observed in malignant tumor tissue, suggesting a coordinated redox response of breast tissues in a normal-weight state. A similar mirror image was previously shown for cancer-associated fibroblasts. Activated fibroblasts exhibit a slight increase in antioxidant defense, following phenotypic change that promotes cancer aggressiveness [33, 35,73,74]. Such "redox coupling" could serve to sustain metabolic cooperation between cancer and its associated stromal tissues [36,74]. There is evidence for metabolic cooperation between adipocytes and cancer cells, but this was not further addressed so far in the redox-dependent context. To the best of our knowledge, we show the redox profile of cancer-associated adipose tissue for the first time and propose that the Nrf2 signaling pathway plays a role in establishing such "activated" phenotype.

Compelling differences in redox profile between normal-weight and overweight/obese women suggest that malignancy-related redox response of adipose tissue differs in obesity. If the increase in AD enzyme expression, found in breast adipose tissue of normal-weight women, is due to pressure imposed by cancer cells, the question of what happens in overweight/obese women remains. Are adipocytes in obesity immune to this induced prooxidant state, or is their ability to respond to it impaired? Malignant tumor-associated adipose tissue in overweight/obese women showed significantly reduced antioxidant capacity and stronger immunopositivity for 4-HNE modified proteins compared to normal-weight women. An increase in 4-HNE was reported as a biomarker of localized prooxidant state [17,75–77] and an inter- and intracellular redox signaling mediator of metabolic reprogramming in adipose tissue of obese individuals [78,79]. Recently, increased 4-HNE release from obese adipose tissue and Nrf2-dependent proliferation of breast cancer cells upon 4-HNE treatment was shown in two independent studies [80,81]. Here, in paired biopsies from obese women, we observed high Nrf2 expression in malignant tumor tissue, concomitantly with high immunopositivity for 4-HNE modified proteins in malignant tumor-associated adipose tissue.

This study's cross-sectional nature does not permit us to discuss temporal relations between obesity and breast cancer or whether described redox differences in tumor and adipose tissue are related to the risk of cancer development or severity of disease progression. Multiple studies showed that obesity reduces breast cancer risk in premenopausal women, contrary to the increased risk in postmenopausal

women [1–5]. Still, there is substantial evidence that obesity leads to higher mortality, shorter disease-free intervals, and increased chemotherapy resistance in pre- and postmenopausal women [6,82]. Our future efforts will be directed towards studying redox-related protein expression and localization in the context of breast cancer tissue architecture and cancer cell and adipocyte ultrastructure. Studies regarding metabolic reprograming of breast tumor tissue and its associated adipose tissue, especially in the context of metabolic cooperation between cancer cells and adipocytes, are needed to expand our current understanding of the redox-driven relationship between mammary adipose tissue, neoplastic transformation, and obesity in premenopausal women.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgment

Abbreviations

Antioxidant defense AD
Copper, zinc superoxide dismutase CuZnSOD
Manganese superoxide dismutase MnSOD
Catalase CAT
Glutathione peroxidase GSH-Px
Reactive oxygen species ROS
White adipose tissue WAT
Body mass index BMI
Superoxide anion $O_2^{\bullet-}$
Hydrogen peroxide H_2O_2, Nuclear factor erythroid 2-related factor 2 (Nrf2), 4-hydroxy-2-nonenal (4-HNE)

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