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Advanced glycation end products and breast cancer: a review of the literature

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ABSTRACT

Advanced glycation end products (AGEs) are mediators of chronic inflammation, which is recognized as an underlying process in carcinogenesis. The role of AGEs in cancers is the focus of recent studies. Breast cancer (BC) is the most common cancer in the world and the etiology is unknown, but some risk factors have been defined; including obesity and diabetes. Both of these disorders are linked to AGEs; thus, BC and AGEs might be associated. AGEs in the human body either derive from the glycation of proteins and lipids in the blood, or from the dietary AGEs (dAGE). AGEs are mainly associated with disease states or aging, including diabetes mellitus, cardiovascular and cerebrovascular disorders, Alzheimer, renal failure, arthritis, skin problems, viral infections, and osteoporosis. Some bioeffects of AGEs are consistent with the chain of events that occur during carcinogenesis. However, the studies about the role of AGEs in specific cancers are not conclusive, and some recent literature, especially clinical studies do not support the theory of the association between AGEs and cancers,. There does not exist a great deal of studies about the role of AGEs in BC, but the subject has been addressed recently. The present evidence is rather in favor of the association of AGEs and breast cancer; however, the direction and type of this association are unclear. In-vitro studies show that AGEs promote features of invasiveness in BC, but clinical studies show diverse findings. In this study, we present an overview of the core existing knowledge about AGEs and their relation with diseases; then provide a brief review of the results of studies that have investigated the association of AGEs and cancer, and then proceed to a concise discussion about studies on AGEs and BC.

Keywords: Advanced glycation end products, Breast cancer, Carcinogenesis, Diet, Glycosilation

INTRODUCTION:

Advanced glycation end products (AGEs) are compounds that have been recognized as one of the intermediary substances in the etiopathology of aging and some diseases [1]. Also, AGEs are mediators of inflammation, and chronic inflammation is known to be an underlying process in the course of carcinogenesis. Therefore, the role of AGEs in different cancers has been the subject of studies in recent years [2].

Breast cancer (BC) is the most common cancer in the world, and the first cause of cancer death among women [3]. The etiology of this cancer is not known, but several risk factors and associated disorders have been defined in this regard; among them, obesity [3, 4] and diabetes [5] Both of these entities have been highly linked to AGEs, and these associations have boosted the possibility of the association between BC and AGEs.

In this study, we first present an overview of the core existing knowledge about AGEs and their relation with diseases; then provide a brief review of the studies that have investigated the association of AGEs and cancer; and finally, proceed to a concise discussion about studies on AGEs and BC.

Definition and sources of advanced glycation end products

Glycosylation is an enzyme-mediated reaction that occurs in normal metabolism, and consists of the programmed addition of a carbohydrate to a protein; generating a functional protein. In contrast, glycation is the non-enzymatic binding of a random reducing sugar to proteins, lipids, or nucleotides in the bloodstream, producing substances with impaired function or durability. AGEs in the body either derive from this endogenous source, or from the intake of AGEs by food. However, the former is also dependent on the latter, as a high carbohydrate diet increases the substrates for AGE production. Dietary AGE (dAGE) is present in many nutrients, but it is higher in processed or flavored foodstuff, as well as roasted, grilled, and fried food [1, 6].

The activity of AGEs is mediated through various cells' receptors, among which, the RAGEs (receptor for AGEs) are more involved [2].

AGEs are mainly associated with disease states or aging, and their main effect is mediated through the activation of chronic inflammatory reactions; ending in cellular and tissue damage, and functional impairment [1, 2].

Diseases associated with AGEs

The role of AEGs in disorders is explained by two primary mechanisms including the crosslinking of circulating and extracellular matrix components. The mentioned processes can promote the damaging and malfunctioning of proteins and cells, and also they can trigger the initiation of cascade reactions leading to oxidative stress activation besides immune responses and inflammation [2, 7, 8].]

The main diseases that have been linked with AGEs are diabetes mellitus and diseases connected to the aging process, including cardiovascular and cerebrovascular disorders, Alzheimer, renal failure, arthritis, skin problems, viral infections, and osteoporosis. Also, charges have been laid against AGEs in regard to the main complications of diabetes including diabetic neuropathy, retinopathy, and nephropathy [7, 9, 1].

Cancer and AGEs

Some bioeffects of AGEs are consistent with the chain of molecular and cellular events that occur during carcinogenesis. These effects consist of long-term pathologic structural changes in cells and their physiologic activities due to the crosslinking of proteins, induction of oxidative stress due to the amplified production of reactive oxygen species (ROS), and stimulation of RAGEs [9]; the latter by itself can increase the proliferation of cancerous tissue, reduce apoptosis leading to increased cancer cells longevity, enhance angiogenesis, and increase the number of RAGEs [2, 8, 10]. As all these events also occur in the microenvironment of malignant cellular transformation and growth, AGEs have been considered as a carcinogenic factor, and even as a cause for metastasis in some studies [2]. In addition, it is worth noticing that throughout the transfiguration of

a pre-malignant lesion to frank cancer, even the genetic and epigenetic conversions are dependent on inflammation mechanisms and ROS that could be the consequence of AEGs accumulation [1].

The key point in these considerations is that the level of AGE in the body is partly dependent on dAGE intake and on lifestyle, thus the association of a western diet, low physical activity or a sedentary lifestyle with cancers can be accounted for [1, 9].

However, the pool of studies about the role of AGEs in specific cancers is not full of conclusive studies, and some recent literature does not support the theory of the association between AGEs and cancers.

From 1997 to 2005, multiple in-vitro studies investigated the presence and association of RAGE with melanoma [11] and cancers of the lung [12], pancreas [13], stomach [14], biliary tract [15], colon [14], mouth [16] and prostate [17]. Although these confirmed the expression or overexpression of RAGE, they were all performed on cell lines. Other in vitro studies have treated animal or cultured cancer cells with AGEs or RAGE inhibitors and assessed their effects over the malignant growth. The studies have found that AGEs promote the proliferation of cultured colorectal cancer and hepatoblastoma cells [18], and pancreas adenocarcinoma cell lines [19]. These positive association detected in in-vitro studies has been a trigger for further real-life investigation.

Epidemiologic studies have considered this subject by using data from large-scale cohorts, and have demonstrated quite different results. Jiao et al [20] investigated the relation of serum AGEs with pancreatic cancer, and detected an inverse association, but reported that dAGE was linked to a modest increased rate of pancreas adenocarcinoma in men in another of their studies [21];they also explored the pre-diagnosis status of dAGE and serum AGEs in colorectal cancer cases [22] and did not find a direct association. A similar study on pancreatic cancer [23] also released negative data, and the results of another study on colon cancer mortality were the same. An indirect association of serum AGEs with hepatic cancer [24, 25] and a direct association with biliary cancer were also reported [25]. The two most updated and large-scale studies in Japan [26] and Europe [27] did not document any significant association between dAGE and overall cancer risk.

Some clinical studies have also addressed the subject. In the first study performed on actual cancer specimens by Vanheijst et al [28] in 2005, AGEs were measured by immunohistochemistry in only five samples of four types of cancers (leiomyosarcomas, laryngeal, breast, and colon cancers). This study showed different levels of AGES in each type of cancer, and the authors concluded that they had been able to demonstrate the presence of AGEs in malignant tissue, but more studies were needed. Foster et al [29] studied the serum and tissue concentrations of AGEs in patients with either low-grade or high-grade prostate cancer, versus normal men. In addition to detecting a higher amount of staining in tumor tissues compared to the normal tissues, they also found a higher level of serum AGE in high-grade cancer cases compared to low-grade ones. Nonetheless, the sample size was small and consisted only of 26 serum samples and 8 tissue samples. Yang et al [30] found increased levels of serum AGEs in men with prostate cancer. Sasahira et al [31] studied the expression of RAGE on cancers of the head and neck, and found a direct association between RAGE expression and risk of recurrence. Rahimi et al [32] found higher levels of RAGE in ovarian cancer specimens than adjacent normal ovarian tissue, especially in those with poor-prognostic features.

Jing et al [33] found that the levels of blood and tissue AGE were indirectly associated with lung cancer, confirmed by Wang et al [34]. Kong et al [35] found no association between serum AGEs and colon cancer and a direct association with rectal cancer, but a nested study within a large cohort by Aglago et al [36] found an indirect association between serum AGEs and colorectal cancer. Wang et al [37] demonstrated that RAGE was overexpressed in gastric cancer tissue, and was positively associated with poor-prognosis variables.

Thus, up to now, despite the positive results of in vitro studies for an association between AGE or RAGE and cancers, epidemiological and clinical studies have

shown substantial contradictory results, with a preponderance of negative results (see Figure 1).

Breast cancer and AGEs

There does not exist a great deal of studies about the role of AGEs in BC, but the subject has been addressed recently.

The issue was first investigated on cell lines. Ishibashi et al [38] were interested about the inhibitory effect of metformin on BC development, and carried out a study on MCF-7 BC cell lines to explore the mechanism underlying this issue, supposing that AGEs might be involved. Meanwhile, they demonstrated that cancer growth was significantly induced by AGEs, and was prevented by metformin [38]. Sharaf et al [39] aimed to investigate the role of AGEs and RAGE in BC, and performed their study via treating a hormone receptor (HR) negative BC cell line with bovine AGEs. They detected an enhanced cell proliferation and increased invasive characteristics of the malignant cells, as well as an amplified expression of RAGEs on the cells after addition of the AGEs. Lee et al [40] cultured triple negative BC cells derived from fresh specimens, and treated them with bovine AGEs. They reported an enhanced cell proliferation and invasiveness induced by AGEs. Pan et al [41] performed a study on BC cell lines by adding AGEs to the culture, and showed that the higher the dose of the exposure, the more severe the invasiveness of the cells, and the higher the rate of RAGEs expression . Nass et al [42] meant to evaluate whether the levels of AGEs in BC tissue could be a prognostic marker, and assessed both histologic specimens and cell lines of BC. As in the above studies, they detected an association between BC and AGEs. However, unlike previous results, they showed that a higher level of AGE was associated with a better prognosis, and an improved response to systemic treatments.

A few clinical studies have also been held about the subject. In a cohort study, Pan et al [43] investigated serum AGE levels of women who had got BC in the follow up

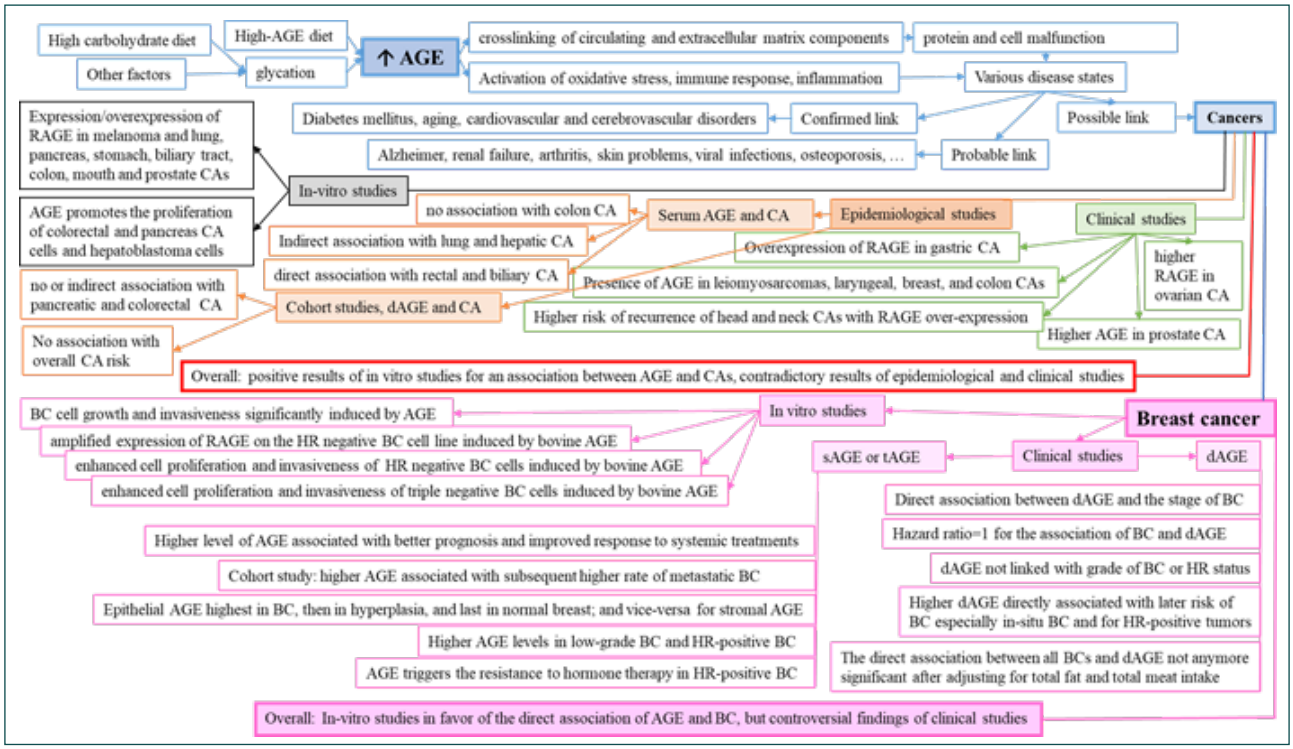

Figure 1. Outline of present information about the relation of advanced glycation end products and breast cancer. AGE=advanced glycation end product, BC= breast cancer, CA= cancer, dAGE= dietary AGE, HR= hormone receptor, IHC= immunohistochemistry, RAGE= receptor for AGE, sAGE= Serum AGE, tAGE= Tissue AGE

period, and found that higher levels of the marker were associated with a higher rate of metastasis. Walter et al [44] compared AGE levels of normal breast, benign breast disorders, and BC in epithelial and stromal tissue; and serum and tissue AGE in HR-positive versus negative and low-grade versus high-grade BC. They also explored the role of AGE in resistance to hormone therapy. Their results were not uniform: they discovered that epithelial AGE was the highest in BC, then in hyperplasia, and last in normal breast tissue; however, the opposite was seen for stromal AGE. They also detected higher AGE levels in low-grade tumors and in HR-positive BC; these are somewhat in accordance with the findings of Nass et al [42]. In the last part of their research, they demonstrated that AGE boosted the resistance to hormone therapy in HR-positive BC.

The association of dAGE and BC has been considered in a few studies. Omofuma et al [45] followed a large group of healthy women who were participating in the intervention arm of a clinical trial about the efficacy of cancer screening. The women had filled a standard food frequency questionnaire at the point of entry, and the researchers assessed the association between levels of dAGE and the risk of BC after 11.5 years. They found that higher dAGE was directly associated with the risk of BC, and this link was higher for in-situ BC and for HR-positive tumors. On the contrary, the study of Peterson et al [46] showed that dAGE was not linked with the grade of BC or its HR status. Also, after adjusting for total fat and total meat intake, the direct association found between all BCs and dAGE was not significant anymore, but there was a direct association between dAGE and the stage of BC. In line with this study and opposite to their previous study, in their last large-scale research incorporating many types of cancer, Cordova et al [27] detected a hazard ratio near to 1 for the association of BC and dAGE, and thus ruled out their previous finding. To sum up (see Figure 1), the present evidence is rather in favor of the association between AGEs and breast cancer; however, the direction and type of this association are unclear. In-vitro studies show that AGEs promote features of invasiveness in BC, but clinical studies show diverse findings. On one side, AGEs trigger BCs with favorable molecular characteristics; on the other side, they increase their invasiveness by inducing resistance to hormonal treatment, and on the other hand, they provoke metastasis. An association between dAGE and BC also is not probable, according to two large studies [46, 27]. In conclusion, the current literature is far from ascertaining a definite unidirectional link between BC and AGEs, and the contribution of dAGE in this process is not unequivocal. Further robust studies are needed to determine and confirm this association and its direction.

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Abbreviation list

AGEs= Advanced glycation end products
BC= Breast cancer
dAGE= Dietary AGE
HR= Hormone receptor
RAGE= Receptor for AGE
ROS= Reactive oxygen species

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