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ORIGINAL ARTICLE

Associated alterations of protein oxidation and cytokines levels in breast cancer

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ABSTRACT

Background: Breast cancer is caused by breast tissue malignant cells and it has become one of the main medical concerns with a socio-economic significance especially for women. Among the multiple factors involved in the initiation, progression, and invasion of breast cancer, oxidative stress plays an important role. Protein oxidation is defined as the covalent modification of a protein, induced either directly by reactive oxygen species/reactive nitrogen species or indirectly by reaction with secondary by-products of oxidative stress. Considerable research shows that the abnormal expression of cytokines plays a key role in the occurrence and development of ovarian cancer, which may be due to the expression imbalance of varieties of cytokines**. Objective:** This study designed to evaluate the role of serum protein oxidation and cytokines marker in the diagnosis of breast cancer.

Methods: A total of 88 females (mean age = 58.6 ±8.7 yrs) with clinically and pathologically confirmed breast cancer were recruited by self-selection. Controls consisted of 58 females. Serum from the patients and controls were assayed immunoenzymatically for protein oxidation markers and cytokines. ELISA test was used for detection of serum ,3-nitrotyrosine (3-NT) ,advanced oxidation protein products (AOPP) , Various cytokines (IL-1, IL-8, IL-10, IL-12 and IL-17)

Results: The levels of 3-nitrotyrosine (3-NT) and advanced oxidation protein products (AOPP) were significantly higher in the study group than in the control group ($P<0.01$) compared to the control group, serum levels of all cytokines (IL-1, IL-8, IL-10, IL-12 and IL-17)were significantly higher in the study group than in the control group ($P<0.001$,) 0.0033, 0.004, 0.001, < 0.001)respectively.

Conclusion: High protein oxidation is an important risk factor for breast cancer. The results indicate that an aberrance imbalance of cytokine production was associated with pathophysiology of breast cancer and cytokine profiles may be applicable as early diagnostic indicators.

Key words: Breast cancer, cytokines, protein oxidation .

INTRODUCTION

Breast cancer is one of the heterogeneous cancer diseases which is caused by breast tissue malignant cells with diverse clinical symptoms and molecular profiles. The disease causes a serious decline of the quality of life (especially in women) and it has become one of the main medical concerns with a socio-economic significance [1]. Nevertheless, and despite its importance, the etiology and pathogenesis are not completely clear. The effects of some of the main effective factors including human races, family history, age, physical activity and obesity, reproductive factors, hormone therapy, and the history of benign breast lesions

have been alternately demonstrated in the incidence of breast cancer [2].

Taking the above information into account, the present study was to evaluate the oxidative stress in Breast patients on the basis of oxidative stress parameters of proteins oxidation,Protein oxidation is defined as the covalent modification of a protein, induced either directly by reactive oxygen species/reactive nitrogen species or indirectly by reaction with secondary by-products of oxidative stress. Protein carbonyls are the most commonly measured products of protein oxidation.

Additionally, nitrotyrosine is a product of tyrosine nitration mediated by reactive nitrogen species such as peroxynitrite anion and nitrogen dioxide. Proteins are one of the major targets of reactive oxidants in cells, and oxidative stress and some other pathological conditions are accompanied by the accumulation of oxidized proteins. Many different types of protein oxidative modifications can be induced by ROS. One of these is carbonylation which is an irreversible, nonenzymatic modification of proteins. ROS can react directly with the proteins, or they can react with molecules such as sugars and lipids, generating products (reactive carbonyl species) that may react with proteins and lead to the formation of protein carbonyl derivatives [3].

Protein-bound 3-nitrotyrosine (3-NT) has been recognized as an important biomarker of nitroxidative stress, associated with inflammatory and degenerative diseases, and biological aging [4].

Cytokines play an important role in the functioning of the immune system. Studies have reported an increased secretion of inflammatory cytokines by the neoplasms. Inflammation plays a role in the pathogenesis of various diseases; it is also a risk factor for the development and progression of a neoplasm, as exemplified by the development of cancer in the region of the head and neck in response to chronic inflammation caused by irritants present, e.g. in cigarette smoke. Cytokines (IL-1 beta, IL-6, TNF, IL-8, IL-17), which take part in the inflammatory response and are, therefore, strongly involved in the development of cancer. The combined action of cytokines produced by the neoplastic cells via multiple mechanisms, modulates cell response of the host immune system. Clinical observations suggest that cancer patients show a progressive disorder of the immune system, resulting in tumor progression. The mechanisms conducive to the weakening or lack of an immune response to neoplastic antigens contribute to the severity of the invasion of cancerous lesions. Although mechanisms that occur between tumor cells, the micro-environment of the tumor and immune cells of the host are not thoroughly known, previous research point to the importance of this interaction in oncogenesis, which may ultimately affect the prognosis[5].

Many researchers point to the participation of these proteins in the development of a neoplasm. Cytokines play a role at all stages of carcinogenesis, induce changes in the tumor microenvironment allowing its further development, and they regulate the immune response. On the one hand, many studies have shown the significant role of cytokines in inhibiting cancer; on the other hand, its promotion and spread. A progressive disorder of creation and operation of cytokines occurs during the development of neoplastic disease. The individual elements of the neoplasm have the capacity to secrete numerous cytokines, which allow an autocrine growth of cancer cells and further development of cancer [6,7].

The purpose of this investigation was to examine the associations between plasma cytokine levels as well as markers of protein oxidation and the presence of breast cancer.

METHODS:

This study enrolled 88 breast cancer patients with pathologically verified breast carcinoma, aged from 29-91 years with the mean age of (65.32 ±11.72) years, through the period from September2022 till April 2023 (58 from oncology unit of Rizgari Hospital , 30 from Nanakaly Hospital cancer and blood diseases . Also 45 apparently healthy women were involved in this study as a control group with mean age of (50.91 ± 9.11) years. The control group was selected from healthy individuals who had no benign or malignant lesions in the breast detected by mammography, who had no disease history, medication use, smoking and alcohol use habits. All study subjects gave written informed consent for their participation in the study. Subjects completed a self-administered questionnaire concerning general and lifestyle characteristics (e.g. age, height, weight, smoking, and drinking), as well as personal and family medical history. Sampling was by self-selection following the approval of the study protocol by the respective Hospitals Ethical Committee, informed written consent obtained from the individuals and exclusion criteria applied. Breast tumour patients who received any therapy prior to diagnosis

(surgery/radiotherapy/chemotherapy),previous history of malignancy and history of any other medical illness, which would otherwise limit the survival of the patient in the absence of malignancy, were excluded. All patients underwent standard treatment modalities (neoadjuvant or adjuvant chemotherapy, radiotherapy, chemoradiation, and/or surgery; depending on the stage of presentation. Blood samples before their treatment (breast cancer cases) or during their health checkup (healthy controls).Following an overnight fast, 5 ml of venous blood was taken from selected patients between 8 A.M. and 10 A.M. The samples were allowed to clot and serum was immediately separated by ultracentrifugation taking full precautions to prevent hemolysis. The supernatant was discarded and the rest of the sample was stored at -20 degrees Celsius.

Biochemical parameters immunoassay

All procedures and reagent preparation were done according to instruction of manufacturer included with Enzyme-Linked Immunosorbent Assay (ELISA) kits. Cytokine kits were purchased from Ray Biotech, Inc. USA.Protein oxidation marker kits were purchased from Immunotech Sas-France.

The simple Step ELISA employs a labeled capture and detector antibody which immunocaptures the sample analyte in solution. This entire complex (capture antibody /detector antibody) is in turn immobilized in the well by immunoaffinity via the anti-tag antibody. Sample or standard are added to wells, followed by the antibody mix. After incubation, the wells are washed to remove unbound material; the TMB substrate is then added.The reaction is stopped by addition of stop Solution which stops the colour development and completes any colour change from blue to yellow. Signal is generated proportionally to the amount of bound analyte and the intensity is measured at 450 nm.A standard curve was constructed for each method using the respective standard and use for the determination of unknown respective serum sample concentrations.

Statistical Analysis

Data were analyzed using statistical GraphPad prism version 9.0 software. For Windows. The findings of Statistical tests and Bar graphs were expressed as mean ±SD. The studied parameter means were compared among the patient and control groups using a parametric independent t-test. Statistical significance was set at $p < 0.05$.

RESULTS

Protein oxidation Parameter in Serum

Protein oxidation parameters including 3-nitrotyrosine (3-NT|) and advanced oxidation protein products (AOPP) are listed in Table 1 The results showed that The AOPP level in BC patients was increased significantly as compared to the controls ($P<0.001$). The concentration of 3-Nitrotyrosine (3-NT) was also significantly higher in BC patients than in controls

Serum levels of cytokines:

Various cytokines (IL-1, IL-8, IL-10, IL-12 and IL-17) were profiled in the serum levels of patients with breast cancer (patients group) and healthy women (control group). Table. 2 shows the serum levels of the various cytokines quantitated in this study. Levels of all cytokines in the sera of the patients group were significantly higher than those in the control group.

Table (1): Comparison of serum protein oxidation levels in serum of patients with Breast Carcinoma and Healthy Controls

parameters	Patients (n=88) Mean ± SD	Control(n=58) Mean ± SD	p-value
Advanced oxidation protein products AOPP(µg/L)	0.43513 ±0.2110	0.0987± 0.0253	< 0.001
3-Nitrotyrosine (3-NT) (ng/L)	236.14 ± 45.61	40.36 ± 6.54	<0.001

Table (2): Comparison of cytokines levels in serum of patients with Breast Carcinoma and Healthy Controls.

parameters	Patients (n=88) Mean ± SD	Control(n=58) Mean ± SD	p-value
IL-1(pg/mL)	56.31 ±29.57	30.7±5.2	< 0.001
IL-8(pg/mL)	23.3±3.6	0.2±0.2	0.0033
IL-10(pg/mL)	4.6 ±1.5	0.2±0.1	0.004
IL-12(pg/mL)	22.4 ±1.3	9.2±1.5	0.001
IL-17(pg/mL)	56.89 ± 45.41	36.43 ± 32.34	< 0.001

DISCUSION

During oxidative stress, protein is more prone to oxidative modification than carbohydrates and fats and accumulates in the body. Advanced oxidation protein products are the final oxidation products of various proteins. They are cross-linked products of serum albumin-based proteins oxidized by hypochlorous acid or chloramine generated by activated phagocytic cells in the process of chlorination and oxidation. AOPPs are considered to be a specific marker for protein oxidization and have a double tyrosine structure characteristic of oxidized proteins[8].

It is widely recognized that oxidation of proteins plays an essential role in the pathogenesis of a large number of degenerative diseases and cancers.Carbonyl group formation is considered an early and stable marker for protein oxidation. The concentration of protein carbonyl is quantitatively stable, and appears to reflect disease endpoints in a biologically significant way. Moreover, increased protein carbonyl has been found in CRC patients[9]. Recently, a new marker of protein oxidation, advanced oxidation protein products (AOPP), has attracted attention of some investigators[10]. AOPP are elevated in patients with cancer where they correlate with markers of oxidative stress[11]. In the study, the level of AOPP and protein carbonyl was increased, demonstrating the presence of oxidative stress in CRC patients. To the best of the knowledge, the study represents the first one to examine the relationship between serum AOPP and the risk of breast cancer.

Advanced oxidant protein products, first described by Witko-Sarsat et al. in 1996[12] further have been hypothesized to activate the endothelial cells and to a lesser extent, fibroblasts to generate reactive oxygen species. Furthermore, advanced oxidation protein products generated by different oxidation patterns lead to the production of either NO or, H_2O_2 suggesting their role in the generation of different types of reactive oxygen species that set a cascade of reactions with a potential to damage cellular micro-molecules eventually turning out into frank oral squamous cell carcinoma[13].

3-NT has also been identified as an indicator of oxidative protein damage and inflammation. 3-NT is a product of tyrosine nitration mediated by reactive nitrogen species such as peroxynitrite anion and nitrogen dioxide. A protein carbonyl assay was not performed in hemolysate because of the significant interference of hemoglobin. Instead,3-NT levels, another indicator of oxidative protein damage, were measured in erythrocyte proteins [14]

Proteins that have been oxidized could give rise to oxidized amino acids and change amino acid side chains that include reactive carbonyls [15]. The attachment of a nitro group to the ortho position of tyrosine residues, which results in the production of nitrotyrosine, is the prime component of peroxynitrite's attack on proteins. In vivo, 3-NT has been employed as a marker for nitrative damage [16]. According to the results of the current research, the patients with breast cancer had significantly greater levels of 3-NT in their serum. This outcome is consistent with what other studies have discovered. [17] found that people with stomach cancer have increased amounts of serum 3-NT

Concentration of 3-nitrotyrosine has previously been examined in tissue sections of ovarian tumors [18]. The nitro-tyrosine expression could already be estimated in benign and borderline ovarian tumors, and high nitro-tyrosine levels in ovarian tumors are linked with poor survival. Current results reveal a similar effect; tumors with high nitro-tyrosine expression had an evil survival in ovarian cancer.It has been reported that the expression of nitro-tyrosine was more elevated in ovarian carcinomas, showing an over 80 % expression [19].

3-nitrotyrosine (3-NT) and Advanced oxidation protein products (AOPP) are oxidation-generated products. Their serum levels were shown to be significantly elevated in OC patients. This suggests that patients with breast tumors have serious protein oxidation damage.

Most cancers arise with the association of chronic inflammation and contain inflammatory infiltrates [20]. Immune cell have broad impact on tumour initiation,growth, and progression and many of these effects are mediated by profile cytokines. Among these cytokines, the pro-tumourigenic function of tumour necrosis factors (TNF-α), IL-6, IL-1, IL-12 are well established [21].

The major pro-inflammatory cytokine, which alone or in combination with other cytokines induces acute and chronic inflammatory conditions is IL-1 beta. This cytokine stimulates chemotaxis in monocytes and neutrophils, activates lymphocytes and osteoclasts and stimulates host cells (fibroblasts, epithelial cells, neutrophils) to produce more enzymes which are destructive to tissue. The increase in concentration occurs in response to an infection, damage to cells, activation of relevant antigens. It is secreted by various cell types, mainly by macrophages. IL-1 beta is involved in local and general inflammatory response, together with IL-6 and TNF. IL-1 beta may activate NF-kB in a manner similar to TNF. IL-1 beta belongs to the family of IL-1 which induces the genes supporting tumor growth and metastasis. IL-1 beta strongly promotes carcinogenesis. It is responsible for the expression of adhesion molecules, increased production of prostaglandins, the release of chemokines [22], whereby there is cell chemotaxis, blood vessel formation and an increase in cellular adhesion, and thus further development of the tumor. There are some studies suggesting that it can contribute to cell proliferation, angiogenesis, and metastasis of various tumors occurring in humans [23].

Overexpression of IL-1 beta contributes to gallbladder cancer tumorigenesis via Twist activation [24]. Its elevated concentrations are found in various tumor types. The increase in IL-1 concentration has been shown in oral cancers, lung, colon, breast, and skin cancers and melanoma [25, 26]. It has been shown that tumors that secrete IL-1 beta are characterized by poor prognosis [27]. The increase in IL-1 beta correlated with tumor progression . The expression of IL-1 beta was observed in 90% of cases in invasive breast cancer and a high concentration of the cytokine in the tumor microenvironment is associated with higher malignancy and more aggressive phenotype [28]. Changes caused by IL-1 beta (from macrophages or from breast cancer cells) produce osteoprotegerin that contributes to increased invasion [28].

Interleukin 1 (IL-1); another pro-inflammatory cytokine strongly expressed by monocytes, tissue macrophages, dendritic cells, B lymphocytes and NK cells refers to two proteins encoded by two different genes (IL-1a and IL-1b), both of which share the same cell surface receptors. The IL-1 signaling via its receptors generates local and systemic responses to injury and infection, thereby inducing fever, pain, sensitivity, vasodilatation, hypotension and slow wave sleep; essential processes towards the re-establishment of tissue homeostasis.

The role of interleukin-1 (IL-1) as determining factor in the immune and inflammatory responses to tumors cells [29] [30] and the ability of IL-1 to induce IL-8 expression in-vitro using human breast cancer (HBC) cell lines [31] has been demonsrtrated. The IL-1 cytokines are present in HBC tissue and homogenates; likewise IL-1 receptors (IL-1Rs) and IL-8 and correlate with prognostic indicators in HBC tumor microenvironment. The activation of the IL-1/IL-1R cytokine family via autocrine and/or paracrine mechanisms leads to a cascade of secondary pro-tumorigenic cytokines, induce the expression of numerous pro-tumorigenic activities such as the expression of IL-8, and subsequently contribute to angiogenesis, tumor proliferation and tumor invasion. A highly significant association exists between the (+3954) T allele of IL1-B gene and the aggressive phenotype of breast carcinoma as defined by the high histological grade, axillary lymph node metastasis and large tumor size [32,33].

Previous studies also demonstrate that tumor-associated IL-1α +, IL-1β are present in the tumor microenvironment and may play a pivotal role in regulating breast tumor growth and metastasis. The expression of interleukin cytokines (IL)-1α,IL-1β, and IL-1 receptor antagonist (IL-1ra) in human breast cancer (HBC) tissue has been demonstrated [34]. The absence of significant difference in cytokine level across disease groups and stages may probably be due to abundance of IL-1 receptors in this racial/ethnic group.

IL-8 produced by the tumor cells increases the influx of neutrophils around the tumor, which in turn produce the compounds that contribute to tumor growth and progression [35] and include respiratory bursts, associated with neutrophil, and the formation of excess reactive oxygen species in the environment of the tumor that can increase the number of secondary mutations of tumor cells [36]. IL-8 can directly stimulate cell proliferation, differentiation of endothelial cells [37]. This

cytokine is able to provoke tumor cell proliferation by activating downstream signals of epidermal growth factor receptor. IL-8 can regulate tumor metastasis through the cyclin D1 signaling pathway [38]. In addition, TNF as IL-1, IL-6 can stimulate the secretion of angiogenic cytokines by other cells [39].

IL-8 induces the expression of metalloproteinases associated with the extracellular matrix, as shown in respect IL-8 induces the expression of metalloproteinases associated with the extracellular matrix, as shown in respect of melanoma, hilar cholangiocarcinoma and prostate cancer [40]. Tumor-associated endothelial cells (TEC) may be an important source of IL-8 in HCC microenvironment. In the study, they postulated that IL-8 secreted by TEC may facilitate the transendothelial migration of tumor cells [41].

IL-8/IL-8R (interleukin-8/interleukin-8 receptors) can modulate tumor cells by activating a epithelial-mesenchymal transition (EMT). EMT can increase stemness, metastatic dissemination and intrinsic resistance. IL-8/IL-8R can change leukocyte infiltration into the tumor that can provoke the dysfunction of cytotoxic antitumor immune cells [42].

A study of pancreatic cancer confirmed the role of proinflammatory cytokines such as IL-6, IL-8 in cancer progression and metastasis . Results of preliminary tests in patients with squamous cell carcinoma of the larynx or with colorectal cancer showed the relationship of IL-8 serum level with the stage of severity [43].

It has been established that the endogenous IL-12 modulates the tumour promoter stimulation of inflammatory responses and may be another possible reason for insignificant TNF-α result in the present work. The development of chemical-induced (DMBA/TPA) skin tumours has been found to diminish in IL-12 knockout mice than in their wild counterparts. IL-12 can possibly influence the expression of the pro-inflammatory cytokines.. Interleukin (IL-12) may be a possible tumour marker in clinical diagnosis and prognosis in breast cancer and cancers in general.

IL-10 concentration is frequently higher in the serum of breast cancer patients compared with normal subjects. Elevated IL-10 might inhibit tumor growth by suppressing IL-6 production, based on the inverse correlation between IL-6 and IL-10 levels in cancer patients [44]. IL-10 is overexpressed in ER-negative versus ER positive breast tumors [45]. A correlation between IL-10 level and clinical stage has also been reported [46]—metastatic disease is associated with higher IL-10 levels than nonmetastatic disease, which might contribute to impaired immunosurveillance,favoring tumor development.

Pro-inflammatory cytokine IL-17 may play a significant role in the pathogenesis of various diseases and carcinogenesis, but its impact on the development of disease progression is unknown. IL-17 was first described in 1993. This is an inflammatory cytokine, mainly secreted by Th-17 (secondary cells T17). Due to the secretion of large amounts of IL-17 byTh-17, most activities of Th-17 are attributable to this cytokine. In addition to Th-17, IL-17 is also secreted by a subpopulation of T lymphocytes CD8+, gamma-delta cells, mast cells and NK cells [. A meta-analysis found that the increase in IL-17 can be correlated with poor overall survival (OS) and disease free survival (DFS) in gastrointestinal tumors [47]. The presence of IL-17 is considered a negative factor in patients with hepatocellular carcinoma and non-small cell lung cancer, the preferred agent for esophageal squamous cell carcinoma and ovarian cancer [48].

The study indicated that IL-17 can induce the production of IL-6, VEGF, prostaglandin E1 and E2, matrix metalloproteinase MMP in the cells of surrounding tissues, leading to inflammation and recruitment of neutrophils and macrophages which act as pro-angiogenic factors in the tumor, promoting cancer growth and progression [49]. IL-17 produced by the transformed enterocytes affect the development of colon cancer by activating ERK, p38 MAPK and NF-kappa B signaling. On the other hand, IL-17 inhibits regulatory T cells (Treg) in the tumor microenvironment and affects the effector activity of the cytotoxic lymphocytes (CTLs) by demonstrating antitumor activity [50].

In ovarian cancer, where elevated levels correlated with a better prognosis, it was found that IL-17 in association of with interferon gamma (IFN-gamma) induced more chemokine TH-1 type CXCL9/10, which was associated with the inhibition of angiogenesis and progression [51]. The researchers suggest that the effect of IL-17 may depend on the immune status of the patient, the severity of cancer, immunogenicity of the tumor and its microenvironment . Th-17 cells are involved in inflammation due to the induction of IL-6, IL-8, COX-2 inhibitors, MMP-1, MMP-3, CXCL1 NOS-2, the epithelial cells, endothelial cells, macrophages and fibroblasts [52]. These compounds are responsible for angiogenesis, tumor growth and metastasis. A

study by Kesselring et al. [53] demonstrated that Th-17 cells are always present in a higher concentration in HNSCC tumors regardless of the stage of the disease. A release by the tumor cells and the TILs, IL-6 and IL-23, and IL-1 beta by immune cells infiltrating the tumor occurs in the HNSCC tumor microenvironment. IL-1 beta and IL-6 induce Th-17, and IL-23 results in the proliferation of Th-17.

Kesselring et al. studied the presence of Th-17 cells in patients with squamous cell carcinoma of the head and neck. Increased number of cells producing IL-17 in the peripheral blood, tumor tissue and the regional lymph nodes and proliferative HNSCC angiogenesis disorder in the presence of Th-17 cells has been demonstrated in these patients, which suggests that Th-17 cells (producing a pro-inflammatory cytokine IL-17) may have a significant impact on the development and progression of HNSCC [53].

Anti-apoptotic and pro-angiogenic activities of IL-17 can promote tumor growth, but can also support the functioning of effector cytotoxic T lymphocytes (CTL), thereby enhancing the anti-tumor response [51]. Many studies have assessed IL-17 in solid tumors for its prognostic value. Some studies indicate its association with tumor progression and poor prognosis [54, 55]. However, there are also papers which indicated that there is no relationship of this cytokine with prognosis or it was suggested that a high level of IL-17 in the blood of patients or in tumor tissue had a relation with improved OS and DFS [56].

The study by Wang et al. demonstrated that mast cells are the predominant cell type secreting IL-17 in esophageal squamous cell carcinoma [57]. The density of cells secreting IL-17 in muscle layer (the muscularis propria) was inversely proportional to tumor invasion and was a factor of a favorable prognosis. This may suggest that mast cells may play a significant role in the immune response to the tumor (tumor immunity) by release of IL-17 in squamous cell carcinoma of the esophagus. However, Sun et al., in a study of juvenile nasopharyngeal angiofibroma (JNA), found that patients who have numerous cells producing IL-17 had significantly higher rates of recurrence [58]. Large infiltration of cells producing IL-17 in JNA microenvironment is an independent negative factor for shorter disease free survival (DFS). The IL-17 function in the development and progression is not completely understood.

CONCLUSION:

In conclusion, oxidative stress is more prevalent in breast cancer patients and may have a significant impact on the development of the disease. It has also been proposed that oxidative stress activates fibroblasts and endothelial cells to produce reactive oxygen species. Additionally, advanced oxidation protein products produced by various oxidation patterns result in the production of either NO or H_2O_2, suggesting their role in the generation of various types of reactive oxygen species that have the potential to damage cellular micro-molecules and ultimately result in oral squamous cell carcinoma.

The levels of selected pro-inflammatory cytokines produced by immune-competent and tumor cells in serum or saliva of cancer patients that are present in the microenvironment of the tumor in primary cultures of tumor cells and in experimental systems for tumor cell lines are the subject of numerous studies in the literature.

Pro-inflammatory cytokines are a poor predictive factor in the majority of clinically occurring malignancies, but they are a favorable prognostic factor in a distinct minority, according to a review of the literature .Analyzing cytokine levels would help with treatment planning and management as well as evaluating the efficacy of used therapies. It could assess a person's vulnerability to the illness and act as a predictor of cancer.

Researchers propose analyzing the cytokine concentrations in oral cancer patients' saliva. Some interleukins, such as IL-1, IL-8, IL-10, IL-12, and IL-17), were generated by breast cancer cells.. The diagnostic accuracy (sensitivity and specificity) measures of inflammatory cytokines in the case of breast cancer in the population at elevated risk for this cancer, however, still require additional research. Tests of cytokine concentrations in serum could be used as an additional non-invasive diagnostic tool to follow patients throughout and after therapy, which would ultimately enhance prognosis and treatment outcomes. Although the mechanisms underlying this interaction between tumor cells, their microenvironment, and immunocompetent host cells are not fully understood, prior studies and clinical observations have shown its significance in tumorigenesis, disease progression, therapeutic response, and potential prognostic implications

Conflicts of interest

The authors declare that they have no conflict of

interest

Financial disclosure: None

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