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Inflammatory markers in cancer: Potential resources

Richa Chauhan[1], Vinita Trivedi[2]

[1]Corresponding Author, Department of Radiation Oncology, Mahavir Cancer Sansthan and Research Centre, Khagaul Road, Phulwarisharif, Patna 801505, Bihar, India, [2]Department of Radiation Oncology, Mahavir Cancer Sansthan and Research Centre, Khagaul Road, Phulwarisharif, Patna 801505, Bihar, India

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1. ABSTRACT

Cancer is a leading cause of death worldwide and a major burden on developing and less developed countries of the world with limited resources for prevention and effective treatment of cancer. Although cancer is multifactorial in origin, various epidemiological and experimental studies

suggest that chronic inflammation has an important role in all stages of cancer, from initiation to progression and even survival of the patient. Inflammatory products like cytokines, chemokines, leucocytes, prostaglandins, cyclooxygenase, reactive oxygen and nitrogen species, metalloproteinase induce genetic and epigenetic changes in normal cells damaging its DNA, inhibiting its repair, altering transcription factors, preventing apoptosis, and stimulating angiogenesis, and thus resulting in carcinogenesis. Thus, these inflammatory mediators have a potential role to become cancer biomarkers for all stages of cancer as many of them can be measured in a cost-effective manner. However, large scale prospective trials are required to validate these potential cancer biomarkers. Nonetheless, a transition from potential to practical utilization of these markers will be an effective tool for the amelioration of cancer burden and mortality in a resource limited setting.

2. INTRODUCTION

Cancer is a leading cause of death worldwide and to add to the existing burden of 18.1 million new cases and 9.6 million cancer deaths in 2018 as per GLOBOCON, the number of cancer cases and deaths is expected to grow rapidly (1). Both ageing and growth of population along with adoption of lifestyle behavior that increases cancer risk can be attributed to the expected increase in the burden of cancer (2). Parallel to the increase in the number of cases, recent years have also witnessed a remarkable progress in the basic, translational and clinical research in cancers. Cancer is now proven to be a multifactorial cluster of diseases involving uncontrolled cell growth and proliferation altering the normal cell behavior. A comprehensive understanding of the altered molecular mechanisms and cellular processes underlying the biological process of carcinogenesis has provide a connecting link between cancer biomarkers and their clinical utility in the comprehensive management of cancer from diagnosis, treatment to prognosis (3). Widespread application of proven cancer control measures, screening, early detection, appropriate therapy with proper follow-up, and prediction measures through cancer biomarkers could definitely be very effective tools for the amelioration of cancer burden and mortality (4).

A biomarker, or biological marker, is in general a substance used as an indicator of a biological state. It is a characteristic that can be measured and evaluated as an indicator of normal biological processes, pathogenic processes, or responses to a therapeutic intervention (5). The use of biomarkers in medicine has been much more extensively studied in oncology than in any other diseases. With the availability of complete human genome sequence, and advancement in key technologies such as high throughput DNA sequencing, microarrays, and mass spectrometry, the plethora of potentially informative cancer biomarkers has expanded dramatically beyond the classical tumor markers to include the sequence and expression levels of DNA, RNA, and protein as well as metabolites (6). Though these genomic and proteomic technologies are quite promising and can significantly enhance the efficacy of cancer management by facilitating the individualization of therapy and also by providing tools for predicting/monitoring therapeutic response; their use is limited to few big cancer centers across the world (7,8). The major hindrance to their widespread use includes the infrastructure required and the associated high cost. Further, issues regarding quality control methods and procedures also need to be developed for using these markers with reliability and reproducibility across the world and especially in low resource developing and under developed countries with a major burden of cancer patients (9).

Epidemiological and experimental data suggest a close connection between inflammation and carcinogenesis (10,11). Inflammation impacts almost all stages of carcinogenesis (12). Molecular and cellular pathways, which connect inflammation and cancer, have also emerged as attractive targets for prevention and therapy (13). The process of inflammation releases a number of markers in the blood which are inexpensive to test and routinely measured in day-to-day oncological practice, and hence potentially provide readily available information to help oncologists to estimate patient prognosis. Nonetheless, one of the major challenges for oncology research is to establish the definite relationship between cancer biomarkers and cancer

pathology in addition to the development of targeted therapies targeting the exact altered cellular process (14).

In this review we intend to discuss general mechanisms and concepts of inflammation causing and promoting cancer and the potential role of inflammatory mediators as cost-effective prognostic biomarkers of cancer with some clinical evidence.

3. CANCER AND INFLAMMATION

3.1. Historical background

The recognition of inflammation as a biological process dates way back to the 1st century A.D. It was defined by A.C Celsius, the Roman physician as the tissue response to injury that results in rubor (redness, due to hyperemia), tumor (swelling, caused by increased permeability of the microvasculature and leakage of proteins into the interstitial space), calor (heat, associated with increased blood flow and the metabolic activity of the cellular mediators), and dolor (pain, in part due to changes in the perivasculature and associated nerve endings) (15). Based on detection of inflammatory infiltrates in solid malignancies, Rudolf Virchow was probably the first person to report a possible association between inflammation and cancer in the mid of 19th century (16). Few decades later, Dvovak *et al* showed that carcinogenesis and inflammatory conditions share common pathways like proliferation, enhanced angiogenesis, increased cell survival and migration. Moreover, they are controlled by the same growth factors, pro inflammatory cytokines and pro angiogenic factors. Further finding of inflammatory cells in cancer tissue lead to the concept of cancer as a “wound that does not heal” (17). Recently, extensive research has been done to unravel the cellular and molecular pathways involved in this complex biologic response of the body to injury, irritation or infection. This has shown that acute and chronic inflammation have different effects in context to carcinogenesis, while acute inflammation and its associated products may protect the body against cancer; chronic inflammation is a facilitating process for many cancers. It is now known that these cellular and molecular products of chronic inflammation lead to several diseases including cancer (18-20). Besides, other established etiological factors of cancer like smoking, obesity, infections, pollution, and radiation are also known to activate proinflammatory pathways (21).

The development of cancer, referred to as carcinogenesis is a step-wise process which can be functionally grouped into three phases: initiation, promotion, and progression. Initiation is characterized by genomic changes in the cell leading to activation of cellular proto-oncogenes or inactivation of tumor suppressor genes causing irreversible cellular changes. Survival and clonal expansion of these “initiated” cells further promote tumor development. Further, progression encompasses growth in tumor size, local invasion and distant metastasis (22).

3.2. Inflammation and tumorigenesis

Long-standing inflammation secondary to chronic infection or irritation predisposes to cancer (23). Large epidemiological studies have shown its prominent role in cancer of the lung, colorectum, breast, hepatobiliary, cervical, gastric, ovarian etc. (24-26). In general, inflammation induces the release of a variety of cytokines, chemokines, free radicals, prostaglandins, growth factors and enzymes as cyclooxygenase and matrix metalloproteinase. These products of inflammation can cause oxidative damage, DNA mutations and other genetic and epigenetic changes in tissue microenvironment making the cells more prone to malignant transformation (27). However, the exact biological process by which the above-mentioned cause of chronic inflammation initiates carcinogenesis differs and remains somewhat undeciphered. Viral infections are estimated to play a causal role in at least 11% of all new cancer cases diagnosed worldwide (28). One of the most prevalent Oncovirus HPV is known to induce carcinogenesis by getting its E6 and E7 genes integrated into human genes and leading to increased expression of cellular protooncogenes like MYC (29). However, the cancer incidence is much lower than the virus prevalence in human population; which bears a testimony to the fact that only infection with the virus is not sufficient for cancer development. Persistence of viral infection along with chronic inflammation and other co-factors

like immunosuppression and acquired mutations is more relevant in context to carcinogenesis. Persistent viral infection causes chronic inflammatory response which generates reactive oxygen species (ROS) that promotes the acquisition of mutations. The accumulation of these mutations eventually leads to cancer as observed in HBV and HCV infection. HBV and HCV infection triggers inflammatory response in the liver cells causing hepatitis, fibrosis, cirrhosis and finally hepatocellular carcinoma (30).

Likewise, chronic response to lung irritants like cigarette smoke induce chronic inflammation followed by epithelial mesenchymal transition and malignant transformation of human bronchial epithelium causing lung cancer (31). Another important cause of cancer, Obesity is also characterized by a chronic state of low-grade inflammation (32). An obese person has an excess of adipose tissue containing adipocytes and immune cells in the stroma. The interaction between immune cells and adipocytes leads to inflammation and subsequent adipose tissue dysfunction. Persistence of obesity causes chronic inflammation leading to adipocyte hypertrophy, immune cell infiltration, angiogenesis and fibrosis, which promotes tumorigenesis (33). Besides, adipose tissue is also infiltrated by macrophages which secretes mediators like TNF-α, IL-18,12,23 and NF-kB and contributes to the pro-inflammatory tumor environment. These mediators trigger autocrine growth factor cascade by inhibiting proliferation control signals including apoptosis and can initiate carcinogenesis (34). A review of the literature by Franks and Slansky had revealed that 23 different chronic inflammatory autoimmune-related diseases are associated with increased risk for focal or organ-specific malignancies, and specifically, cancer of the organs targeted by the inflammatory condition (35). Celiac disease can be considered as a paradigm for chronic inflammation predisposing patients to cancer development. It targets the gut and is associated with an elevated risk of gastrointestinal malignancies. It is associated with chronic enteropathy and release of factors like IFN-γ and CD8+ T-cell activation, which leads to tissue damage and gut cytotoxicity, creating a pro malignant chronic inflammatory state (36). Similarly, chronic mucosal trauma due to betel nut chewing, ill-fitting dentures, gall stones etc. results in inflammation, thereby releasing chemical mediators such as cytokine, prostaglandins, and tumor necrosis factor. This could induce genetic and epigenetic changes damaging DNA, inhibiting its repair, altering transcription factors, preventing apoptosis, and stimulating angiogenesis, thus resulting in carcinogenesis (37).

3.3. Inflammation and tumor progression

We now know that inflammatory cells and mediators play a critical role in fostering tumorigenesis. Following the transformation of a cell to malignant state; these mediators further support tumor growth by supplying signaling molecules to the tumor environment which include growth factors like EGF that sustain proliferation, pro-angiogenic factors like VEGF-A/C and extracellular matrix-modifying factors like MMP-9 that sustain angiogenesis, facilitates tissue invasion and supports metastatic dissemination (38). In order to maintain the inflammatory environment, the tumor cells itself promote inflammation by recruiting a variety of immune cells to its stroma. It is now proven that virtually every neoplastic lesion contains immune cells present at densities ranging from subtle to gross infiltration. The immune cells include macrophages, mast cells, neutrophils, eosinophils, dendritic cells, as well as T and B lymphocytes (39).

These cells produce a number of mediators which increases cell proliferation. One of the most relevant factors in this context is the TNF-α which acts via the NF κB signaling pathway (40). An increased expression of TNF-α has been found in a number of cancers including breast, bladder, colorectal cancer and also in leukemia and lymphoma (41,42). IL-6 is another typical cytokine with tumor growth effect. It acts by activating the JAK tyrosine kinase and transcription factor STAT-3 pathway, as seen in many cancers like multiple myeloma, colorectal and breast cancer (43 – 46).

A strong relationship has also been documented between inflammation and local invasion in cancer and studies suggest that the most important inflammatory mediators involved in local tumor invasion are the extracellular matrix

remodeling proteinases, such as the matrix metalloproteinases (MMPs) (47). They belong to a family of Zinc dependent proteolytic enzymes that degrade various components of extracellular matrix. MMP-9 facilitates tumor invasion by degrading type IV collagen, a major structural protein component of extracellular matrix and basement membrane (48, 49).

Tumour-associated macrophages (TAMs) constitute a significant component of inflammatory infiltrates in neoplastic tissues (50). They produce a number of cytokines and proteases including potent angiogenic and lymphangiogenic growth factors to accelerate neoplastic progression (51). Activated macrophages producing TGF-β, TNF-α, IL-1α, arachidonate metabolites and extracellular proteases have been found in melanoma patients which induces the melanocytes to produce IL-8 and vascular endothelial growth factor (VEGF)-A, causing vascular angiogenesis (52). It was also reported that macrophage infiltration is closely associated with the depth of invasion of primary melanoma (53). In addition to melanoma, macrophages in cervical cancer patients are also known to express VEGF-C and VEGF-D as well as the VEGF receptor-3, all of which are implicated in formation of lymphatic vessels and lymphatic metastases (54).

Angiogenesis, the development of new capillaries from preexisting blood vessels, is required for tumor growth larger than a 1- to 2-mm diameter and for the development of metastasis. It is not only a hallmark of cancer but also one of the molecular events that links chronic inflammation closely to cancer development and progression (55). Angiogenesis in general, is exacerbated by an increased production of chemokines, cytokines, growth factors, proteolytic enzymes, proteoglycans, lipid metabolites and prostaglandins. These factors enhance angiogenesis through Vascular endothelial growth factor (VEGF) production (56). Another well-known regulator of angiogenesis Angiopoietin 2 can also upregulate inflammatory responses, indicating a common signaling pathway for inflammation and angiogenesis (57). In addition, MMP-9, and members of fibroblast growth factor (FGF) family activated by 5- lipoxygenase are also important in sustaining tumor angiogenesis (58).

Inflammation also plays a regulatory role in the metastasis of cancer cells. Tumor associated macrophages and their mediators influence the multistep process of metastasis, from interaction with the extracellular matrix to homing at a distant site (51). Monocytes are also important component of the metastatic cascade as they release a number of proangiogenic and metastatic factors like VEGF, FGF-2, platelet derived growth factor (PDGF), intracellular adhesion molecule (ICAM-1), vascular cell adhesion molecule (VCAM-I), E-selectin, P-selectin and MMP-9 (59).

Thus, it is now evident that inflammatory cells and their products have a powerful impact on the process of tumor development, growth, invasion, angiogenesis and metastasis. Once initiated, both inflammation and non-inflammation associated cancer recruit immune cells to maintain the supply of tumor sustaining and promoting inflammatory products. Some of these mediators can be easily measured in blood and tissue samples. These mediators can be used as biomarkers of inflammation and given the close association between inflammation and cancer, can possibly play an important role as biomarkers of different phases of cancer.

4. BIOMARKERS OF INFLAMMATION

4.1. Cytokines

Cytokines are substances which are secreted by various immune cells of the body, predominantly by macrophages and T-lymphocytes. They can be either proteins, polypeptides or glycoproteins, and serve as signaling molecules, mediating and regulating the immunity, inflammation as well as hematopoiesis (60). They include a number of mediators, which are structurally similar but differ in their function. Depending on their function, they can be divided into six groups; chemokines, interleukins (ILs), interferons (INFs), colony-stimulating factors (CSFs), transforming growth factors (TGFs) and tumor necrosis factors (TNFs). Among them, ILs and TNF-α are predominantly pro-inflammatory and critical factors required for transformation, proliferation, invasion, angiogenesis and metastasis. Chemokines are a

subtype of cytokines which are capable of inducing directed chemotaxis of various cells towards the site of inflammation. Four groups of chemokines are found based on the first two cytosine residues on the polypeptide chain. CC chemokines consist of two adjacent cytosine residues at the amino terminus. CXC chemokines consist of two cytosine residues at the N-terminus, which are separated by one amino acid. C chemokines consist of one cytosine in the N-terminus and the other cytosine downstream. CX3C chemokines consist of three amino acids between the two cytosine residues (61). These cytokines exert their carcinogenic effect by activating various signal transduction pathways like NF-κβ, JAK/STAT, MAPK, AP-1 (62). Many of these cytokines have been measured in serum, plasma, tissue and cell culture supernatant in several studies and correlated with cancer risk, stage and prognosis (63-66). However, till date their short half-life, strict collection and storage requirements, and above all lack of specificity have restricted their routine use as cancer biomarkers (67-68).

4.2. Leukocytes

Leukocytes are an integral part of both innate and the adaptive immune system, and include granulocytes (neutrophils, basophils, eosinophils) monocytes, macrophages, dendritic cells and lymphocytes (B&T cells), which can exert both immune stimulating or immune-suppressive functions. When activated they also release a number of cytokines and tumor growth promoting factors (69). The leucocyte profile of the body changes with stages of inflammation and serve as potential biomarkers of inflammation. A complete blood count (CBC) is the most common routinely performed simple blood tests in clinical practice and is available everywhere. Several studies have successfully correlated a shift in the number or ratio of these routinely measured blood parameters with risk, stage and prognosis of cancer. The measurements include neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR) and platelet to lymphocyte ratio (PLR) (70-72). Tumor infiltrating lymphocytes (TILs), white-blood cells found within the tumor which presumably reflect an immune response against the tumor have also been extensively studied recently and usually incorporated in histopathological reports (73). With their widespread use, ease of measurement, low cost, and ample evidence they have the best potential to be developed as cancer biomarkers for different stages (from predicting risk, response to therapy and survival) in clinical practice, as shown in various studies (70, 74-76). However, large prospective trials incorporating their use is still required.

4.3. Acute phase proteins

Acute phase proteins are a group of serum proteins which are synthesized by the liver in response to inflammation. These proteins can interact with a number of receptors on macrophages in the tumor environment and potentially modulate them to increase tumor cell survival, growth and metastasis. Its production is regulated by endothelial cells, activated monocytes and macrophages. C-reactive protein and Serum Amyloid A are the two important Acute phase proteins involved in the process of tumorigenesis and progression (77). Though they can be measured easily in blood, their level can be altered by transient conditions like acute infections and trauma which limits their practical application as a cancer biomarker. Multiple serial measurements are therefore recommended to track changes in levels over time (78-79). Glasgow Prognostic Score (GPS) and modified Glasgow Prognostic Score (m GPS), using a combination of albumin and CRP level in the patient have also been used as a prognostic marker in cancer patients (80-81).

4.4. Reactive oxygen and nitrogen species

Reactive oxygen (ROS) and reactive nitrogen species (RNS) are free radicals that are produced as a result of inflammation. Their formation is stimulated by cytokines through activation of protein kinase signaling cascade (82). ROS and RNS also recruit additional inflammatory cells leading to generation of more ROS and RNS, and thus forming a vicious cycle. An excess of reactive oxygen and nitrogen species lead to oxidative and nitrosative stress (83). This causes damage of DNA, proteins, lipids and carbohydrates which can have mutagenic effects on the cells. Oxidation and nitrosative deamination of nucleobases present in the DNA by

ROS and RNS respectively causes altered replication, transcription and translation which exert oncogenic effects (84-85). These free radicals also lead to lipid peroxidation whose products again react with DNA and are mutagenic (86). Two important such products which can be measured and are documented to be associated with an increased cancer risk are trans-4-hydroxy-2-nonenal (HNE) and malondialdehyde (MDA) (87-88). In addition, ROS also triggers the release of factors like vascular endothelial growth factor promoting angiogenesis (89). So, though directly related to etiology and progression of cancer these inflammatory markers are extremely difficult to measure as they have a very short half-life in nanoseconds. Consequently, their products like MDA and etheno-DNA adduct are quantified in plasma, urine and tissues using high performance liquid chromatography (HPLC), immunoprecipitation and fluorescence detection methods (90).

4.5. Prostaglandins, cyclooxygenases, lipoxygenases and related factors

Prostaglandins are a group of lipid compounds that are enzymatically derived from essential fatty acids as a part of inflammatory response. Cyclooxygenase (COX) enzyme catalyzes the formation of four distinct group of prostaglandins from arachidonic acid namely Prostaglandin E (PGE), Prostaglandin F (PGF), Thromboxane (PGA) and Prostacyclin (PGI). The enzyme cyclooxygenase has two isoforms COX-1, the constitutive form and COX-2, the inducible form. In addition, the fatty acids are also modified by the lipoxygenase enzymes (ALOX). The lipoxygenase pathway produces leukotrienes from macrophages (91). Among the two pathways, it is the cyclooxygenase pathway and the prostaglandins which have been studied for its association with carcinogenesis and cancer progression. The major role includes immunosuppression, inhibition of apoptosis and promotion of angiogenesis. Immunosuppression is mainly mediated by PGE which suppresses mediators such as T and B lymphocytes, lymphokines, natural killer cells, cytotoxic T cells, and macrophages. Thromboxane, PGE and Prostacyclin produced from endothelial cells further induce Interleukin 6 and haptoglobin which are important mediators for angiogenesis and invasion (92). Apoptosis or programmed cell death is a controlled mechanism for destroying cells with genomic alterations that have oncogenic potential and is a major protective mechanism against cancer development. This process is mediated through the tumor suppressor gene p53 and inhibited by bcl-2. The induction of this anti-apoptotic protein, bcl-2 by PGs in the tumor microenvironment is a major factor in the avoidance of apoptosis by cancer cells and uncontrolled tumor growth (93). The direct measurement of the level of prostaglandins in body tissues have been tried but it involves labor intensive sample preparation and is not very specific (94). So, it is the quantification of expression and level of COX 2 by immunohistochemistry in tissue which is clinically used to measure these mediators or biomarkers (95).

4.6. Transcription factors and growth factors

The carcinogenic effects of the various inflammatory mediators are mediated through various growth and transcription factors. These factors are proteins that bind to cellular and nuclear receptors to elicit a downstream response (96). The two most important transcription factors central to the initiation and progression of cancer are Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ) and Signal transducers and activators of transcription (STAT3). Activation of either NF-κB or STAT3 is found in over 50% of all cancers and is a pre-requisite for the expression of a variety of target genes important for tumorigenesis (97-98). NF-κB activation in inflammatory cells in response to infectious pathogens, pro-inflammatory mediators as well as necrotic cell products results in the production of factors that support growth, survival, and vascularization of pre-malignant and malignant cells. The NF-κB family comprises homo- and heterodimeric transcription factors consisting of RelA, c-Rel, RelB, NF-κB1 (p50 and its precursor p105), and NF- κB2 (p52 and its precursor p100) with RelA-p50 as being the most prominent NF-κB transcription factor (99). Activation of NF-κB up-regulates cell cycle mediators (cyclinD1, c-Myc), anti-apoptotic (c-FLIP, survivin, bcl-2, bcl-xl, IAP-1, IAP-2), adhesion molecules (ICAM-1, ELAM-1, VCAM-

17), proteolytic enzymes (MMP, uPA), and pro-inflammatory factors (PGHS-2, cytokines) that promote an invasive phenotype and the presence of its constitutively active form in cancer patients has been found to be associated with poor clinical outcome (100-102). Further, the constitutive activation of STAT-3, does not only promote cancer-related inflammation but also suppresses anti-tumor immune responses. Studies have shown that both STAT-3 and NF-κB interact at multiple levels and together boost tumor-associated inflammation. STAT -3 acts as a co-transcription factor for NF-κβ, Re1A by increasing its nuclear life. On the other hand, numerous RelA-encoded target gene products like IL-6, IL-11, IL-17, IL-21, IL-23, PGHS-2 function as STAT-3 activators (62).

5. CLINICAL EVIDENCE FOR APPLICATION OF INFLAMMATORY MARKERS AS CANCER BIOMARKERS

As per GLOBOCON 2018, for both sexes combined, lung cancer is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths), closely followed by female breast cancer (11.6%), colorectal cancer (10.2%), and prostate cancer (7.1%) for incidence and colorectal cancer (9.2%), stomach cancer (8.2%), and liver cancer (8.2%) for mortality (1).

A number of studies have reported an association between presence of inflammatory markers and risk of cancer development. Further, studies have also demonstrated association between level of inflammatory markers in cancer patients and their survival. The literature search in the electronic databases retrieved hundreds of related articles, and we selected those that we thought to be most relevant to our purpose (Table 2).

5.1. Lung Cancer

5.1.1. Etiology

In the Health Aging and Body Composition study by Dora Il'yasova *et al*, the relationships between circulating levels of the inflammatory markers like interleukin-6 (IL-6), C reactive protein (CRP), tumor necrosis factor-α (TNF-α) and site-specific cancer incidence was studied. This prospective study recruited three thousand seventy-five healthy participants including black and white men and women in the age group of 70 to 79 years, whose baseline levels of inflammatory markers were measured in frozen stored serum (IL-6 and CRP) or plasma (TNF-a). A total of 435 cancer events were detected during the follow up period with breast, colorectal, lung and prostate cancer comprising 63% of the total diagnosed cases. The results established a positive association between increased level of inflammatory biomarkers and cancer incidence. All three markers were associated with lung cancer. (24) A nested case-control study within the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial was done to estimate lung cancer risk associated with levels of circulating inflammatory markers (103). It showed 11 markers that represent several components of the inflammation process including acute-phase proteins, cytokines, chemokines, and growth factor to be associated with lung cancer risk (104).

5.1.2. Prognosis

Recent work by Ryan *et al* on a small panel of circulating cytokines identified elevated levels of IL-6, a pro-inflammatory cytokine, as an indicator of poor survival in lung cancer patients (105). With the introduction of screening in lung cancer, many cases are being diagnosed in stage I which is traditionally treated by surgery alone. However, about 20% to 30% of these patients recur after surgery suggesting a need for biomarkers to identify aggressive stage I patients who need adjuvant treatment and spare the relatively less aggressive patients from over treatment (106). With this background, a study was done by Meaney *et al* to explore blood-based inflammatory biomarkers to identify patients at high-risk of mortality for which additional treatment modalities can be offered at time of diagnosis. Their results showed that patients with elevated serum levels of IL-6 and IL-17A have a 5-year survival rate of only 46%, considerably lower than the 93% 5-year survival rate of patients with low levels of IL-6 and IL-17A. The intermediate group, patients with high levels of one of the two markers, also had a significant association with survival and a 5-year survival rate of 73% (107).

5.2. Breast Cancer

5.2.1. Etiology

The Women's Health Initiative study (WHI), is a prospective study that was designed to examine the common causes of morbidity and mortality among postmenopausal women, including cancer, cardiovascular disease, and osteoporosis. Initially, 161,808 postmenopausal women in the age group 50 to 79 at baseline, were recruited from 40 US centers between September 1, 1993 and December 31, 1998 (108). After the original WHI study ended in 2005, the WHI Extension Study (2005–2010) was carried out to collect 5 more years of follow-up data and the second WHI Extension Study (2010–2015) collected an additional 5 years. Among them, biospecimen subsample was available for 22,124 participants and a prospective analysis was conducted among 17,841 healthy postmenopausal women with baseline CRP and Body Mass Index BMI measurements to examine associations of pre-diagnosis high-sensitivity C-reactive Protein (hsCRP) with breast cancer incidence and post-diagnosis survival and to assess whether associations are modified by BMI. The results showed that a 1 SD increase in log hsCRP was associated with 17% increased breast cancer risk among normal weight women (BMI<25), whereas no association was observed among overweight/obese (BMI≥25) women. Similarly, an increased mortality risk was apparent among leaner women with higher hsCRP levels as compared to overweight/obese women. The probable hypothesis given for this difference seen was that other risk factors such as estradiol and insulin that were found to be elevated in overweight/obese women might have masked the increased risk associated with the presence of generalized inflammation (109). Besides, a large meta-analysis of 15 published articles by Guo *et al* reported that a single log-unit increase in circulating CRP was associated with a 16% increase in breast cancer risk (110)(Table 1).

5.2.2. Prognosis

Cellular-mediated inflammatory products like lymphocytes, neutrophils, and monocytes are increasingly being recognized as having an important role in carcinogenesis. In this context, studies particularly in breast cancer (BC) have suggested that a high neutrophil-to-lymphocyte ratio (NLR) along with other similar haematological indices like Platelet to lymphocyte ratio (PLR), Lymphocyte to Monocyte (LMR) is associated with shorter survival. Dirican *et al.* studied the role of pre-operative NLR as a prognostic factor in 1527 patients with BC with a follow-up of nearly 6 years. They concluded that there was a significant difference regarding disease free survival (DFS) and overall survival (OS) in patients with NLR <4 and NLR ≥4 (respectively, $P < 0.00$, $P < 0.001$) (111). A meta-analysis by Chen *et al* to evaluate the association between NLR and overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS) or cancer specific survival (CSS) showed high NLR to be a significant negative prognostic factor in breast cancer patients (112).

Besides haematological indices, A study by Denkert *et al* suggested that the presence of tumor-associated or infiltrating lymphocytes (TIL) in breast cancer is a new independent predictor of response to anthracycline or taxane based neoadjuvant chemotherapy and provides useful information to identify a subgroup of patients with a high benefit from this type of chemotherapy (113).

5.3. Prostate cancer

5.3.1. Etiology

On the basis of a strong clinical background linking chronic prostatitis to prostate cancer, epidemiological studies studying the correlation between inflammatory markers and prostate cancer have largely shown that inflammation plays a role in initiation and progression of prostate cancer (114). In particular, there is strong evidence that the cyclooxygenase enzymes (COX 1 and 2), the enzymatic targets of most non-steroidal anti-inflammatory drugs (NSAIDs), are involved in the initiation and promotion of prostate cancer (115). A meta-analysis by Mahmud *et al* to study the association between use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) and the risk of prostate cancer concluded that the protective effect of aspirin and other NSAID use against prostate cancer is only suggestive and not conclusive (116). To further extend knowledge on the role of inflammation in prostate cancer risk, Toriola *et al* investigated the associations between markers of

Table 1. Risk factors causing chronic inflammation and cancer

Risk Factors	Common Examples
Virus	HPV, HBV, HCV, EBV, KSHV, HTLV-1
Bacteria	Helicobacter Pylori, Bacteroids sp.
Protozoa	Schistomiasis
Autoimmune	Celiac disease, Ulcerative colitis, Crohn's disease, Myasthenia gravis, Rheumatic Arthritis, Systemic Lupus Erythematosus
Dietary	Tobacco, Alcohol, High Fat diet
Metabolic	Obesity
Trauma	Areca nut chewing, Sharp teeth, dentures, Gall stones
HPV: Human Papilloma Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; EBV: Epstein Barr Virus; KSHV: Kaposi's sarcoma associated herpes virus; HTLV-1: Human T- lymphotropic virus	

systemic inflammation (CRP, fibrinogen and leukocyte count) and risk of prostate cancer among 2,571 middle-aged men in Finland. They concluded positive associations between leukocyte count and risk of prostate cancer but increased CRP and fibrinogen level was not associated with the risk of developing prostate cancer (117).

5.3.2. Prognosis

Prostate cancer (PC) is mainly treated with surgery in early stage, radiation in both early and locally advanced stage and with hormones in metastatic stage. Shafique *et al* investigated the role of inflammation-based prognostic scores, the modified Glasgow Prognostic Score (mGPS) and neutrophil lymphocyte ratio (NLR), to predict progression after Radical Prostatectomy and concluded that raised mGPS had a significant association with excess risk of death (118). Many clinical data on the relationship between inflammation and response to radiotherapy for PC are present in the literature. Markers like NLR, PLR, CRP have been studied and their increased levels have been found to be associated with poor survival as they create a microenvironment favouring cancer proliferation and metastases despite radiotherapy (119). Recent studies also confirm that systemic inflammation represents a truly novel and unexplored prognostic variables in castration resistant metastatic prostate cancer (CRPC), which is independent of other clinical parameters such as stage. These markers do not substitute but rather integrates with established prognostic factors. Studies have shown both NLR (cut-off value 2-3) and CRP (cut-off value 8) as an independent and significant predictor of overall survival and progression free survival in CRPC cases receiving chemotherapy with Docetaxel and NLR for patients being treated with abiraterone (120-122). A critical review on Prognostic value of inflammation in prostate cancer progression and response to therapeutic by Sciarra *et al* concluded that various inflammatory parameters that can be easily obtained from the blood/serum can be integrated with established prognostic factors to formulate validated prognostic algorithms (123).

5.4. Colorectal cancer

5.4.1. Etiology

The Health Aging and Body Composition study showed that IL-6 and CRP were associated with the risk of developing colorectal cancer (24). A study by Ghuman *et al* is perhaps the largest population-based study assessing common inflammatory markers and colorectal cancer. This study included a large cohort of men and women aged 20 years and older in greater Stockholm area with serum C-reactive protein (CRP), albumin, haptoglobin and leukocytes measured between 1986 and 1999. These serum inflammatory markers were investigated in relation to colorectal cancer incidence and subsequent survival. During a mean follow-up time of 18 years, 4764 out of 325 599 participants (1.46%) developed invasive colorectal cancer. An increased risk of colorectal cancer was found to be associated with higher levels of haptoglobin and leukocytes, Further, a borderline inverse association was reported with albumin and no association was

Table 2. List of some routinely measured systemic inflammatory markers which have been used as cancer biomarkers

Inflammatory Marker	Explanation	Reference
Lymphocyte/Monocyte Ratio (LMR)	• Lymphocytopenia has been associated with increased tumor burden and poor prognosis. The probable cause could be destruction of lymphocytes by tumor cells which decreases body's anti-tumor response • Monocytosis has also been found to be associated with poor prognosis as they Tumor associated macrophages, which is an important mediator of cancer progression and metastases. • The division of lymphocyte count by monocyte count is defined as LMR. • A low LMR as a simple biomarker of host immune system, has been suggested to be related to poor prognosis in various cancers. • The median cut-off value for LMR has been reported to be 3.0	70
Neutrophil/ Lymphocyte Ratio (NLR)	• The neutrophils act as tumour-promoting leukocytes, capable of suppressing anti tumour immune response; are effectors of angiogenesis; promote leakage of tumour cells and endothelial cells into the circulation, therefore contributing to participate in metastatic cascade. Therefore, an elevated neutrophil count can stimulate tumour angiogenesis and contribute to disease progression, thus leading to a negative correlation between neutrophil density and patient survival. • On the other hand, lymphocytes are a part of host's antitumor response the presence of lymphocytes in the tumour is associated with better responses to chemotherapy and better prognosis. • Thus, the NLR can reflect the balance between the activation of the inflammatory pathway and the antitumour immune function. • The division of neutrophil count by lymphocyte count is defined as NLR. • An increase in NLR has been reported to correlate with poor prognosis in cancer patients. • A cut-off value between 2-4 has been reported in various studies.	74
Platelet/ Lymphocyte Ratio (PLR)	• Platelets are another important tumor promoting leucocytes. They secrete vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet derived growth factor (PDGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), transforming growth factor β (TGFβ), and many cytokines which promote epithelial to mesenchymal transition (EMT) and promote metastasis. • Lymphocytes, as we know are part of host's defense against tumor. • The division of platelet count by lymphocyte count is defined as PLR. • The cutoff values estimated for PLR is 160. • A high PLR value corelates with a poor response to therapy and bad prognosis.	75
Tumor Infiltrating Lymphocytes (TIL)	• Tumor infiltrating lymphocytes are associated with the immune status of host and many studies have shown its presence to be a good prognostic factor. Various methods have been described by different researchers for evaluation and quantification of TILs. They can be measured in the tumor, invasive margin, surrounding stroma on simple H &E stain. An international TIL working group2014 has laid down recommendations for evaluating and reporting TILs. • A high degree of lymphocyte infiltration is predictive of a better response to chemotherapy and good long-term prognosis.	76
Glasgow Prognostic Score (GPS)	• A combination of Albumin and C-reactive protein (CRP) measurements into a 3level predictive score. • Patients who had both a serum elevation of CRP (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were allocated a GPS of 2. • Patients with only one of the abnormal values were allocated a GPS of 1, and • Patients who had neither were allocated a GPS of 0. • Survival decreases with increasing score	80
m Glasgow Prognostic Score (mGPS)	• Similar to GPS, except only hypoalbuminemia is score 0. • Patients who had both a serum elevation of CRP (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were allocated a GPS of 2. • Patients who had only serum elevation of CRP but not hypoalbuminemia were allocated an mGPS of 1, and • Patients who had neither or only hypoalbuminemia were allocated a mGPS of 0. • Survival decreases with increasing score.	81

found with CRP. For colorectal cancer-specific death, the only positive association observed was with haptoglobin. The study concluded that altered levels of pre-diagnostic inflammatory markers may be associated with an increased risk of colorectal cancer and worse cancer-specific survival after diagnosis (124).

5.4.2. Prognosis

A recent review of the literature by Nasr *et al* on the role of inflammatory markers and micro RNAs as prognostic markers for response to systemic chemotherapy and overall survival was done. It revealed a critical role of inflammatory markers especially acute phase proteins, cytokines and blood cell ratios as prognostic markers (125). Multiple studies have evaluated the role of acute-phase reactants, including albumin, CRP, ferritin, fibrinogen, haptoglobin, and D-dimer, on prognosis in both early and advanced CRCs and reported their increased level as a bad prognostic factor (126). Pretreatment serum concentrations of several proinflammatory cytokines like IL-1β and IL-6, and TNF-α may help identify early cancer progression among patients and were found to be independent prognostic factors of overall survival (OS) and Progression free survival (PFS) in CRC patients (127). Various blood cell ratios, such as neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to lymphocyte ratio (PLR), have also been evaluated in predicting the clinical outcomes of colorectal cancer. Kim *et al.* showed that high NLR (≥3.0) is an independent risk factor predicting poor long-term outcomes in patients with stage III and IV, but not in stage I and II (128). A systematic review done by Tan *et al.* included 15 studies and a total of 3991 CRC patients to analyze the relationship between PLR and OS and DFS. This meta-analysis showed that an elevated PLR was significantly associated with lower OS and DFS, poor tumor differentiation, the propensity toward depth of infiltration, and recurrence (129).

Besides, these four most common cancers a number of inflammatory markers have been reported both as risk and prognostic marker in a number of other cancers like ovary, endometrial, renal cell carcinoma, liver, pancreatic, esophageal, stomach, head and neck, lymphomas, melanomas (25, 37, 130-135). A description of all the types and subsites of cancer related to inflammatory markers is beyond the scope of this review.

6. SUMMARY AND PERSPECTIVE

Thus, we see that the biological rationale and the clinical evidence makes inflammatory markers a potential candidate to be a cancer biomarker, which can predict the risk of developing cancer, its prognosis, response to therapy, and also survival. However, when seen in the context of a biomarker, these mediators not only have some advantages but also major limitations. The major advantage includes the availability of a wide spectrum of inflammatory mediators to be measured whose level either alone or in combination can be used as cancer biomarkers. The tests for some of these markers like the haematological indices (NLR, PLR, LMR) is simple, low-cost, validated and routinely done everywhere. Other group of markers like acute phase proteins (CRP, albumin, fibrinogen, haptoglobin etc.) can also be easily measured in blood. Then there are markers like cytokines, prostaglandins, cyclooxygenase and growth factors whose isolation and detection methodologies are complicated, needs expertise and are relatively expensive, but much less when compared to the molecular and genomic techniques. Large scale prospective trials are needed to validate these potential prognostic and predictive markers, as well as to determine their cut-off levels, sensitivity, and specificity in cancer patients with different primary tumor sites. One of the major limitations with these markers is that they are not specific for any tumor type/site and can be found to be raised in a number of other chronic diseases. Because inflammation is a hallmark of carcinogenesis, it is not possible to get a site-specific inflammatory marker.

As we understand, a panel of inflammatory markers should be used in adjunct with established risk and prognostic markers to subclassify the stages of cancer which are more aggressive and would probably benefit from additional therapy. Further,

large studies are required to develop nomograms combining clinical stage, histology, grade, other clinico-pathological parameters with a panel of inflammatory markers to define groups of patients with similar prognosis and response to therapy. These nomograms can then be correlated and validated with available genomic and molecular sub classification of various cancer types before incorporating them into clinical practice. A transition from potential to practical utilization of cost-effective inflammatory mediators as cancer biomarkers will be very helpful for the oncologists of developing and under developed countries of the world in treating cancer patients with limited resources.

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Abbreviations: DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid; HPV: Human Papilloma Virus; ROS: Reactive Oxygen species; HCV: Hepatitis C Virus; TNF-α; Tumor necrosis factor α; IL: Interleukin; NF-κβ; Nuclear factor kappa-light-chain-enhancer of activated B cells; IFN: Interferon; CD: Cluster of differentiation; EGF: Epidermal growth factor; VEGF: Vascular endothelial growth factor; MMP-9: Matrix metallopeptidase 9; JAK: Janus kinase; STAT-3: Signal transducer and activator of transcription 3; TAM: Tumor associated macrophages; TGF-β; Transforming growth factor β; FGF: Fibroblast growth factor; PDGF: Platelet derived growth factor; ICAM-1: Intracellular adhesion molecule 1; VCAM-1: Vascular cell adhesion molecule 1; CSF: Colony stimulating factor; MAPK: Mitogen activated kinase; AP-1: Activator protein 1; CBC: Complete blood count; GPS: Glasgow prognostic score; m GPS: modified Glasgow prognostic score; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; TIL: Tumor infiltrating lymphocytes; CRP: C-reactive protein; PDGF: Platelet derived growth factor; HGF: Hepatocyte growth factor; IGF: Insulin like growth factor; EMT: Epithelial to mesenchymal transition; RNS: Reactive nitrogen species; HNE: trans-4-hydroxy-2-nonenal; MDA: malondialdehyde; HPLC: High performance liquid chromatography; COX: Cyclooxygenase; PG: Prostaglandin; ALOX: arachidonate 12- lipoxygenase; LMR: Lymphocyte to monocyte ratio; OS: Overall survival; DFS: Disease free survival; RFS: Recurrence free survival; CSS: Cancer specific survival.

Key Words: Cancer, Inflammation, Biomarker, Risk Factor, Prognosis, Inflammatory Mediators, Review

Send correspondence to: Richa Chauhan, Department of Radiation Oncology, Mahavir Cancer Sansthan and Research Centre, Khagaul Road, Phulwarisharif, Patna 801505, Bihar, India. Tel: 8002226696, Fax: +91-612-2253957, E-mail: chauhan_richa@outlook.com