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A review of the application of inflammatory biomarkers in epidemiologic cancer research

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Abstract

Inflammation is a facilitating process for multiple cancer types. It is believed to affect cancer development and progression through several etiologic pathways including increased levels of DNA adduct formation, increased angiogenesis and altered anti-apoptotic signaling. This review highlights the application of inflammatory biomarkers in epidemiologic studies and discusses the various cellular mediators of inflammation characterizing the innate immune system response to infection and chronic insult from environmental factors. Included is a review of six classes of inflammation-related biomarkers: cytokines/chemokines, immune-related effectors, acute phase proteins, reactive oxygen and nitrogen species, prostaglandins and cyclooxygenase-related factors, and mediators such as transcription factors and growth factors. For each of these biomarkers we provide a brief overview of the etiologic role in the inflammation response and how they have

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been related to cancer etiology and progression within the literature. We provide a discussion of the common techniques available for quantification of each marker including strengths, weaknesses and potential pitfalls. Subsequently, we highlight a few under-studied measures to characterize the inflammatory response and their potential utility in epidemiologic studies of cancer. Finally, we suggest integrative methods for future studies to apply multi-faceted approaches to examine the relationship between inflammatory markers and their roles in cancer development.

Keywords

Inflammation; biomarkers; neoplasm; cancer epidemiology

INTRODUCTION

The role of inflammation in the development and progression of cancer is of great scientific and public health interest and has drawn much attention of late. Several excellent reviews have described the likely cellular and molecular roles of inflammation in the development of cancer (1-13) and have outlined the consistent associations between chronic inflammatory conditions (14-19) and inflammation-inducing risk factors (such as tobacco (20-22)) in the development of cancer at various sites. As the burden of cancer increases globally (23, 24) so does the value of identifying therapeutic targets. The role of inflammation in carcinogenesis requires additional research to clarify the mediators, pathways and steps through which increased or altered inflammation leads to neoplastic development or progression. Ultimately, continued research is required to identify the key points of potential intervention to successfully improve outcomes. In order to proceed, epidemiologic studies will require integrative techniques across many platforms to elucidate meaningful mechanisms and improve outcomes.

In this review we provide an overview of several effectors of inflammation involving the response of the immune system to infection and to chronic insult from environmental factors. We summarize the commonly used measurements to evaluate inflammatory status or alteration in the development of cancer, including the strengths and weaknesses of the common techniques available for each marker. We have provided recent evidence and findings to date regarding associations with cancer etiology and progression. Our literature summaries are not meant to be exhaustive due to the extent of this field and where possible we refer readers to relevant meta-analyses and literature reviews for concision. Subsequently, we highlight several under-studied measures of the inflammatory response. A general framework for the biomarkers of interest and their inter-relationships with cancer risk is depicted in Figure 1. We suggest integrative multi-faceted approaches for future studies seeking to examine the relationship between the markers and their roles in cancer development. Per definition, we refer to all of the biological measures of the immune and inflammation responses included in this paper as ‘inflammation biomarkers’ for simplicity although there is certainly great variety in the measures discussed.

Methodological Issues in Epidemiologic Studies on Inflammation and Cancer

In the evaluation of the associations between inflammation and cancer risk, careful consideration must be taken to address the potential for biased associations due to the well-known pro-inflammatory potential of tumors and, thus, their microenvironment (6). Prospective studies are, therefore, preferable due to lower risk of presenting temporally biased associations. Prospective designs also allow for latency analyses to determine whether the inflammatory marker associations are causal drivers of carcinogenesis or simply pre-diagnosis manifestation of tumor-related inflammation. Therefore, ideal prospective research designs investigating inflammatory markers should be conducted on samples taken many years, perhaps even decades, prior to diagnosis. Repeat sampling is useful, because of the different mechanisms by which inflammation can drive carcinogenesis, e.g., DNA damage (in earlier years) vs. enhancement of angiogenesis (later). Samples collected only a few years prior to diagnosis may no longer reflect an evaluation of causality of the biomarker, instead becoming an evaluation of an early disease prediction marker, which although still clinically relevant, reflects a different hypothesis. In this context, large population-based cohorts with biobanking initiatives are extremely valuable in evaluating associations of inflammatory biomarkers. In our presentation of the literature we emphasized large, prospective studies over retrospective designs. We also emphasize evidence from biomarkers measured in blood and to a lesser degree urine samples in large epidemiologic studies. Although several protocols exist for measuring target organ-specific inflammation-related compounds in several media including exhaled breath and its condensate (25), sputum (26, 27) brochioalveolar lavage (28), and feces (29) among others (30) at present these biospecimens are prohibitively expensive to feasibly collect in large population-based initiatives.

The inflammation responses under investigation may be due to a multiplicity of factors which have been consistently linked to cancer risk including, but not limited to tobacco consumption (31), overweight and obesity (32, 33), physical inactivity (34, 35), persistent and or transient infection (36) and immunosuppression (37-39). Thus, in a well-designed epidemiologic evaluation of the causality of inflammatory biomarkers during carcinogenesis these factors should be accounted for, depending on which specific biomarkers are being evaluated, in both the design and analysis stages in order to best isolate the causal associations being examined.

In studies of inflammation and subsequent cancer-related clinical outcomes and survival, pre-surgical or pre-treatment blood samples should be collected to avoid the impact of treatment on levels of inflammatory and immune markers. In population-based studies examining inflammatory biomarkers on survival outcomes through active follow-up or passive cancer registry linkage, attention must be taken to collect detailed staging information for adjustment in analysis. Failure to do so invites the possibility of confounding due to a third factor related to inflammation and advanced stage at diagnosis, therefore affecting survival. Below we review six main classes of inflammation-related biomarkers: cytokines/chemokines, immune-related effectors, acute phase proteins (C-reactive protein, Serum Amyloid A), reactive oxygen and nitrogen species, prostaglandins

and cyclooxygenase-related factors, and mediators such as transcription factors and growth factors.

INFLAMMATION BIOMARKERS

Cytokines/Chemokines

Background—During both acute and chronic inflammatory processes, a variety of soluble factors known as cytokines are involved in leukocyte recruitment through increased expression of cellular adhesion molecules and chemoattraction (40-43). To a large extent they orchestrate the inflammatory response, *i.e.* they are major determinants of the make-up of the cellular infiltrate, the state of cellular activation, and the systemic responses to inflammation (44). Cytokines are central in extensive networks that involve synergistic as well as antagonistic interactions and exhibit both negative and positive regulatory effects on various target cells (42). Although produced by a wide variety of cell types, macrophages and T lymphocytes (T-cells) are the primary producers of cytokines which may have predominantly pro-inflammatory (inflammation-promoting)(IL-1α, IL-1β, IL-2, IL-6, Il-8, IL-12, TNF-α, IFN-γ(45)) or anti-inflammatory (inflammation-suppressive)(IL-4, IL-5, IL-10, TGF-β) abilities.

Measurement—The measurement of cytokines as an indicator of inflammatory status in population-based initiatives is an area of great promise, yet provides several challenges due to the biochemistry of the molecules, particularly their short half-life (46, 47). Considering the immediate response of the body to injury, it can be advisable to draw the blood tube that is dedicated for cytokine measurements first during a blood draw. Cytokines can be measured in serum and plasma samples however, measurements from the different sample types cannot be used interchangeably (48, 49). They can also be measured in tissues or as supernatant from cultured peripheral blood mononuclear cell (PBMC) preparations (50). Cytokine measurements can be multiplexed to simultaneously assess multiple targets (51), presenting the opportunity to broaden the scope of investigation or test for possible interactions between the mediators. These techniques are, however, limited by differential concentrations of the varying cytokines. In addition cytokine quantification can be affected by degradation through freeze/thaw cycles over longitudinal storage (52). Also, issues of standardized sample collection, processing and study design must be carefully considered or sensitivities in the protein measurements may create artifactual associations if care is not taken (46). Concentrations of cytokines are known to vary in different tissues and a standard blood draw may not adequately reflect tissue-specific levels of inflammation (53). However, measurements of circulating cytokines may provide a general sense of an individual's inflammatory state. Additional advantages and disadvantages to measurement of cytokines are summarized in Table 1.

Cancer Associations

Risk: Systemic cytokine concentrations have been associated with both cancer risk (54-57) and cancer progression (58-62) suggesting a pivotal role in carcinogenesis. For example, in the Health, Aging and Body Composition cohort circulating IL-6 and TNF-α were associated with lung cancer (LC), IL-6 was also associated colorectal cancer (CRC),

however, neither were associated breast (BC) and prostate (PC) (62). Investigation of serum IL-6 and IL-8 levels in the Prostate Lung Colon and Ovarian (PLCO) Cancer Screening Trial showed associations with LC (IL-6, Odds Ratio (OR)=1.48, 95% Confidence Interval (CI)=1.04-2.10; IL-8, OR=1.57, 95% CI=1.10-2.24), compared with the lowest quartile. However, increased IL-6 levels were only associated with cancers diagnosed within two years of blood collection, whereas increased IL-8 levels were associated with cancers diagnosed more than two years after blood collection (OR = 1.57, 95% CI = 1.15-2.13) (54). Whether this difference in association is due to cytokine degradation over time or a real association remains to be determined.

IL-10 has been investigated in the development of non-Hodgkin's lymphoma (NHL) in a prospective study with a significant positive association observed (63) as well as with pre-diagnostic levels of IL-10, TNF-α and sTNF-R2 in a separate prospective investigation (64).

Progression: Several studies have observed negative prognosis of various cancers associated with IL-6 level including PC (65), renal cell carcinoma (RCC) (66), non-small cell LC (67), OC (68), lymphoma (69, 70), chronic lymphocytic leukemia (CLL) (71), esophageal (ESOC) (72), CRC and BC (73).

Investigation of prognosis with IL-6 serum concentrations (≥4.0 pg/mL) in the Multiethnic Cohort Study showed associations with significantly poorer survival in both African Americans (hazard ratio (HR)=2.71, 95% CI=1.26-5.80) and Caucasians (HR=1.71, 95% CI=1.22-2.40). IL-10 (HR=2.62, 95% CI=1.33-5.15) and IL-12 (HR=1.98, 95% CI=1.14-3.44) were associated with LC survival only in African Americans (74). Serum levels of IL-6 have also been associated with tumor proliferative activity among patients with CRC (75).

An examination of clinical outcomes among hepatocellular carcinoma (HCC) patients after potentially curative hepatectomy reported that higher pre-therapy serum levels of IL-17 and lower levels of IL-1 were associated with early recurrence. After adjustment for general tumor clinic-pathological factors, elevated serum levels of IL-17 (≥ 0.9 pg/ml) were found to be an independent risk factor for HCC early recurrence with an HR of 2.46 (95%CI=1.34-4.51). Patients with larger tumors (>5 cm in diameter) and elevated serum levels of IL-17 had the highest risk of early recurrence as compared to those with only one of these factors (P = 0.009) or without any (P<0.001). The authors suggest that these factors showed similar effects on the HCC patient overall survival (76).

Immune-Related Effectors

Background

Leukocytes comprise an integral portion of the innate, as well as of the adaptive immune system, and include granulocytes (neutrophils, basophils, eosinophils) monocytes, macrophages, dendritic cells and lymphocytes (B&T cells), which can exert immune-stimulating or immune-suppressive functions (77). In cancer patients, several pathways can be activated to suppress the effective adaptive immune response, triggered to avoid the destruction of the tumor by immune cells (78). Leukocytes also activate to release cytokines

and growth factors, which support tumor growth. The activities of the immune system lead to a change of blood leukocytes profile, which serves as a marker of the systemic inflammatory response. Based on this principle, several measurements of inflammation and a shift in number or ratios of immune cells have been investigated for the association with cancer risk or outcome of the disease such as the modified Glasgow Prognostic Score (mGPS), (79) neutrophil to lymphocyte ratio (NLR) (80) and platelet to lymphocyte ratio (PLR) (81).

Tumor infiltrating lymphocytes (TILs) are white-blood cells found within the tumor which presumably reflect an immune response against the tumor (82). It is thought that TILs work in combination with chemotherapies which can promote cytotoxic T-lymphocytes that can produce anti-tumor immunity and thus lead to improved outcomes (83). However, a role in supporting tumor-growth cannot be excluded. T Helper 17 (Th17) cells are a CD4+ T cell subset in addition to Th1 and Th2 that lead to increased levels of IL-17, IL-22 and IL21 production (84-86). IL-6 and other cytokines including IL-23 are thought to play a key role in the production of the Th17 cells (84, 87, 88). They mediate host defensive mechanisms to various infections through provide anti-microbial immunity at epithelial/mucosal barriers and are involved in the pathogenesis of many autoimmune diseases (86).

Measurement

The measurement of lymphocytes can be performed using tissue, or peripheral blood samples and is based on standard clinical routines (white blood cell [(WBC]) counts). Flow cytometry has also become a widely used tool to quantify phenotypic subsets of immune cells and thus provides a snapshot that allows for some understanding of the current immune response (89-91). Flow cytometry can also be used to quantify T cell proliferation using dyes (92).

Despite great promise, flow cytometry is limited in its epidemiologic application as the experiments are sensitive to issues of standardization particularly from differences reagents, sample handling, instrument setup and data analysis. These differences across study sites are known to effect outcome measurements (91, 93, 94) and have been shown to affect results in multi-centered projects (95). Attention to standardization of procedures along the project pipeline may aid in alleviating these concerns and promote cross-project collaborations which is one of the goals of the human immunology project (96). In addition, the quantification of immune cells generally requires fresh biospecimen, which limits its use in epidemiologic studies.

TIL can be measured by immunohistochemistry (97) using different stains including hematoxylin and eosin and through the use of multicolor flow cytometry (98). TIL can be quantified using tissue microarrays and whole tissue sections (99). Th17 can be measured by multicolor flow cytometry (100) can be evaluated in peripheral blood and other body fluids (101, 102).

Cancer Associations

Etiology—A comprehensive review of the associations between these immunological markers and outcomes is beyond the scope of this review. Briefly, various measures of leukocyte quantities such as WBC count, platelet to lymphocyte ratio (PLR) and the neutrophil to lymphocyte ratio (NLR) have been associated with increased risk of several types of cancer including BC, CRC and EC), but also with tumor progression (81, 103). The WHI (Women's Health Initiative) observed a significant association between WBC count and increased risk of invasive BC, CRC, EC, and LC in more than 140,000 postmenopausal women (103).

Prognosis—Likewise, a study investigating the association between several inflammation-based prognostic scores such as mGPS, NLR and PLR and cancer survival observed strong prognostic values of all three scores for cancer survival independent of tumor site (BC, BLC, OC, PC, gastro-esophageal, hematological, RCC, CRC, NHC, hepatopancreaticobiliary and LC) in more than 27,000 patients (104).

TILs have been the focus of many studies and were shown to be positively associated with improved survival among cancer patients, including CRC (105), LC (106), and others sites (107-109). In addition, the assessments of TIL densities at the margin of liver metastasis of CRC patients were predictive for chemotherapy response (110). CD8+ TILs were independently predictive of improved BC survival however results vary by molecular subtype (improved in basal, but not in triple-negative) (111) and by estrogen receptor status and histological grade (112).

The presence of Th17 cells in OC (113), PC (114), LC (115) and PANCC (116) as well as in melanoma (117) were repeatedly associated with better survival of patients (118).

Acute Phase Proteins

C-reactive Protein (CRP)

Background—CRP is an acute phase protein found in blood, which is synthesized in the liver in response to inflammation. Physiologically the protein activates the complement system via the Q1 complex (119). Once activated, the complement system aids in clearing the injured or dead cells from tissues. CRP has been related to systemic levels of inflammation in various inflammatory conditions as well as chronic diseases such as cardiovascular disease and type II diabetes (120). CRP is also highly related to obesity (generally measured using body mass index in population studies) across genders and study populations (121), although most research has been done on Caucasian populations, as obesity is a chronic inflammatory state/condition (122). Obesity has been associated with cancer risk and progression at various sites with one of the suggested mechanisms to be operating through chronic altered inflammation (32, 33, 123-127). Therefore, CRP may act not as a causal protein but as a marker of systemic inflammation. Elevated CRP levels have also been correlated with other elevated inflammatory markers (128).

Measurement—CRP measurements can be performed in whole blood, plasma and serum using various immunoassays (129) with high sensitivity nephrelometry being the gold

standard. As with other inflammatory markers, CRP has a relatively short half-life, and thus proper sample processing is essential (130). Transient conditions such as a common cold or mild injury/trauma can drastically alter individual CRP levels (131). Thus, variability of CRP levels may lead to issues in analyses and or biased statistical estimates. It is possible to recognize and eliminate infection-induced very high values by reviewing CRP levels against age- and BMI-standardized rates and excluding individuals with a certain level of variability above. Nevertheless, single studies with single measurements can be affected by transient conditions. One investigation into the effects of a single CRP measurement in epidemiologic studies suggested that conducting a single measurement could largely attenuate observed effect sizes from true effect sizes (132). Multiple measurements would therefore be optimal to track changes in levels over time. However, an analyses with repeated measurements has shown that a small index of individuality was observed in healthy individuals with relative rankings over a six month interval differing minimally (133).

Cancer Associations

Etiology: Several prospective analyses have shown that CRP is associated with risk of cancer at various sites (54, 134, 135). An investigation of risk at multiple sites in the Healthy Aging and Body Composition Study showed that baseline levels were associated with LC, CRC and BC risk. A nested case-control study also suggested associations for HCC, LC, skin, RCC, and bladder cancer (BLC) (136). Prospective investigations have observed null associations for BC (137, 138) but increased risk for OC (139).

The association results for CRP and CRC risk, however, are contradictory, as a previous meta-analysis of eight prospective studies suggested that increased CRP levels collected at baseline was related to a modest increase in CRC risk (RR=1.12, 95% CI=1.01-1.25) (134), while, a recent nested case–control conducted in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, observed a 15% reduction in risk of developing colorectal adenoma (OR=0.85, 95% CI=0.75–0.98, P-trend=0.01) (140). A study by Toriola et al. utilizing repeat assessments of CRP in the Women's Health Initiative Observational Study Cohort among 980 women and controls demonstrated that CRP was associated with an increased risk of CRC, however, that the change in CRP over time was not predictive, thus, suggesting little value as an early detection marker (141).

For LC, the associations appear to be consistent across studies. A meta-analysis of 10 studies involving 1918 LC cases showed a pooled RR of 1.28 (95%CI=1.17–1.41) for LC for one unit change in natural logarithm (ln) CRP (142).

Prognosis: CRP has also been shown to be associated with cancer progression (143) and survival (144, 145). Clinical investigations have shown that CRP levels of patients with pancreatic (PANCC), (146) ESOC, (147) PC (148) and NHL had advanced staging (149), higher disease recurrence (150, 151) and shorter and shorter survival, which was also observed for CRC (152).

A meta-analysis of 10 BC studies that involved 4,502 patients observed significantly decreased overall (HR=1.62, 95%CI=1.20-2.18) and disease-free survival (HR=1.81, 95%CI=1.44-2.26) when CRP levels were elevated. For cancer-specific survival, the pooled

HR in higher CRP expression in BC was 2.08 (95%CI=1.48-2.94), which could strongly predict poorer survival in BC (153).

Serum Amyloid A

Background—Serum Amyloid A (SAA) is another acute phase protein similar to CRP. However, circulating SAA levels are thought to be more responsive to inflammation as levels drop off more rapidly following an inflammatory stimulus (154). Unlike CRP, which activates the complement system, to eliminate target cells and induce inflammatory cytokines and tissue factor in monocytes (155, 156), the physiologic effects of SAA are far less understood.

Measurement—SAA is measured in serum, similarly to CRP, using high-sensitivity nephelometry often with micro-latex agglutination tests as the gold standard. Levels can also be detected in saliva using different techniques including fluorescent immunoassays (157).

Cancer Associations

Etiology—SAA has been related to risk at several cancer sites including colon OR=1.5, 95% CI=1.12-2.00 among women (141). Elevated SAA levels have also been highly related to LC risk in the PLCO study as well as gastric cancer in the Japan Public Health Center-based prospective study (158). These analyses have also shown a strong correlation between SAA and CRP, suggesting that measurement of both is essential to control for possible confounded associations and that any independent predictive ability remains to be determined.

Prognosis—SAA is related to stage of disease (159) and strongly associated with reduced long-term survival of BC (160), LC (161) and esophageal squamous cell carcinoma (162). SAA may represent a link between inflammation and metastasis, thereby reducing survival outcomes in CRC (163).

Reactive Oxygen & Nitrogen Species

Background

Reactive oxygen (ROS) and reactive nitrogen species (RNS) are free radicals that are produced as part of the normal metabolic cycle. ROS generation is based on the reduction of molecular oxygen, catalyzed by NAD(P)H oxidases and xanthine oxidase or in a non-enzymatic reaction by redox-reactive compounds of the mitochondrial electron transport chain (164). RNS are produced as by-products of the conversion of arginine to citrulline by nitric oxide synthase (NOS). Both, ROS and RNS are important signaling molecules and involved in metabolism, cell cycle and intercellular signaling cascades, especially in inflammation processes (41), as their formation is stimulated by cytokines and chemokines through activation of protein kinase signaling cascades (165). In a vicious cycle, ROS and RNS recruit additional inflammatory cells, leading to further generation of free radicals. An overproduction of ROS or RNS and limited antioxidative capacities can result in unbalanced metabolism and consequently lead to oxidative or nitrosative stress (166). This is accompanied by damage of DNA, protein, lipids carbohydrates and small metabolites and

can be deleterious for cells, tissues and organisms (14, 165, 167). DNA damage through nitrosative deamination of nucleobases or guanosine peroxidation results in 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG), the addition of a hydroxyl radical to the c8 position of the guanine ring. This alteration can subsequently lead to single- or double-stranded breaks, deoxynucleotide or deoxyribose modifications and DNA crosslinks (168). These genomic alterations can exert oncogenic effects through altered replication, transcription and translation (169, 170). Oxidation of the guanine base is the most abundant DNA lesion and can be a highly mutagenic miscoding lesion (171). Measurement of oxidatively generated DNA damage products in urine has been shown to be useful for epidemiologic studies to quantify inflammatory exposures (172). 8-oxodG is often referred to as 8-hydroxy-2′deoxyguanosine (8-OHdG), however, for consistency in the review we refer henceforth only to 8-oxodG even for those studies who have used the term 8-OHdG. For a discussion of this nomenclature see Cooke et al (173) who recommend this term as it conforms with the International Union of Pure and Applied Chemistry. Furthermore, this is the more appropriate term as the oxidised nucleobase (8-oxoGua) is a tautomer that at physiological pH is mainly present in the oxo-form and not the hydroxy-form.

ROS also leads to lipid peroxidation (LPO) whose products are genotoxic and mutagenic and can react with protein and DNA (174). Two LPO products generated by ROS which have been investigated in cancer etiology are DNA-reactive aldehyde byproducts *trans*-4-hydroxy-2-nonenal (HNE) and malondialdehyde (MDA). These molecules react with DNA bases to form exocyclic DNA adducts (175, 176). Reaction of DNA bases with these LPO end-products yield five-membered rings (etheno-DNA adducts) attached to DNA including 1,N^6-etheno-2′-deoxyadenosine (εdA) and 3,N^4-etheno-2′-deoxycytidine (εdC) (177). εdA and εdC appear to be promising tools for quantifying pro-mutagenic DNA damage in early, premalignant stages of the carcinogenesis process (178). These etheno-DNA adducts can be directly quantified in tissues and urine. They have been implicated in clinical studies (179) and may serve as potential risk markers for associations between inflammatory diseases and cancer (180).

A F2-isoprostane isomer, 8-isoprostaglandin $F_{2\alpha}$ (8-Iso-$PGF_{2\alpha}$), has also been found to be a sensitive and reliable index of *in vivo* oxidative stress reflective of DNA damage through lipid peroxidation (181).

In addition, ROS play a crucial role in angiogenesis by triggering the release of angiogenic factors such as vascular endothelial growth factor (VEGF). Thus, it is hypothesized that ROS are involved not only in developing cancer but also in cancer progression (13, 182).

Measurement

The measurement of reactive oxygen species presents an interesting and challenging possibility to directly quantify the oxidative burden within tissues. ROS/RNS can be measured either directly in several different tissue types (182-184) or indirectly by measuring the product of ROS/RNS reactions. The main limitation to the direct measurement of ROS/RNS is the extremely short half-life with an estimated lifespan of OH component of < 1ns in blood (185). Consequently, most blood and tissue storage protocols used in observational study designs are not feasible. Measurement of H_2O_2 can be measured

directly in urine as a proxy of whole body oxidative stress (186), however, as dietary factors can also raise urinary H_2O_2 (187) associations may be confounded. H_2O_2 can also be measured in exhaled air and breath condensate (188), this however, may not be feasible on a large-scale for population-based studies. Probes such as Dichloro-dihydro-fluorescein diacetate (DCFH-DA) can also be used to detect 'cellular peroxides' in cells (189).

Methods have been developed that assess oxidative DNA and protein damage that results from ROS/RNS using tissue-specific measures of protein residues (190). Oxidative DNA damage can be measured by gas chromatography-mass spectrometry (GC-MS), high performance liquid chromatography coupled to electrochemical detection (HPLC-ECD), HPLC--mass spectrometry (MS) as well as immunoassays and enzymatic assays among others (167, 191).

8-oxodG in urine serve as a reliable measures of 'whole-body' oxidative stress (192, 193) and can be quantified using HPLC-MS (194-196) or HPLC-ECD (197). 8-oxodG and 8-Iso-PGF2_α can also both be measured in Plasma using commercially available ELISA protocols. Of concern for epidemiologic studies is the poor agreement between ELISA and tandem-mass spectrometric HPLC-MS in methodological comparisons of measurements from urine (198-200).

MDA can be quantified in plasma, urine and tissue using several methods including HPL-ECD, GC-MS, LS-ES-MS/MS (201). MDA quantification by HPLC has shown good inter-laboratory validity in replicate human EDTA treated plasma samples sent to multiple labs (202). HNE can also be reliably detected in plasma and urine using both HPLC (203) methods and ELISAs (204).

Etheno-DNA adducts can be directly quantified in tissues and urine (179). εdA can be quantified in using immunoprecipitation/HPLC/fluorescence detection methods (205) and εdC can be quantified using modified thin layer chromatographic protocols (206). HPLC-MS protocols have also been developed to quantify εdA and εdC from a single DNA sample using purified DNA from cells or tissues (207). A recent population-based application of immunoaffinity/32P-postlabeling (208) successfully quantified εdA and εdC from buffy coat collected in a population-based study (EPIC-Heidelberg) suggesting potential utility in larger population-based investigations as a direct measure of exposure related DNA alterations from oxidative stress (209).

Nitrotyrosine, a byproduct of reactions with nitrogen radicals and reactive nitrogen species can be measured in various tissues. 3-Nitrotyrosine can be assayed in serum or from tissue sample using commercially available ELISA kits, however, commercially available kits have provided low reproducibility and conflicting results (210). It can also be measured using electron spin resonance (211), polychromatic flow cytometry (FACS)(212) and GC-MS (213). These techniques have been limited in their application in population-based studies, however, these biomarkers present as an interesting avenue for inflammation quantification projects.

Cancer Associations

Etiology—Epidemiological studies have shown that serum 8-oxodG levels were significantly increased in patients with CRC compared with controls. A Japanese study suggested that levels of 8-oxodG and fibrosis were significant risk factors for HCC, especially in patients with hepatitis C virus infection (214). Several studies have observed either elevated blood (215), urinary or salivary levels of 8-oxodG in oral cancer compared to controls. For example, an investigation of salivary 8-oxodG levels in oral squamous cell carcinoma patients showed a 65% increase compared with controls (216). Urinary 8-oxodG levels were also significantly higher among breast (217, 218) and colorectal (219) cancer patients than among controls subjects in adjusted analyses. Elevated 8-oxodG levels have also been observed in blood from patients with squamous cell carcinoma of the esophagus (220-222) . Elevated 8-oxodG has been associated with a modestly increased risk of BC (IRR: 1.08; 1.00-1.17 per nmol/mmol creatinine excretion) increase) (223) and LC among never smokers (IRR= 1.17 (1.03–1.31)) (224).

Epidemiologic data examining DNA damage using LPO suggest increased 8-Iso-$PGF_{2\alpha}$ is positively associated with risk of breast cancer (225, 226) and colorectal cancer (227). MDA levels have been associated with lung cancer (228, 229). In a prospective investigation of pre-diagnostic serum levels of reactive oxygen metabolites (ROM), specifically hydroperoxides, in the European Prospective Investigation into Cancer and Nutrition cohort (EPIC) ROM were associated with overall CRC risk when comparing highest tertile vs. lowest (adjusted incidence rate ratio (IRR)=1.91, 95%CI=1.47- 2.48). This association was, however, seen only in subjects with relatively short follow-up, suggesting that the association results from production of ROS by preclinical tumors (230). In a study of oral cavity cancer patients lipid peroxidation products such as lipid hydroperoxide (LHP) and malondialdehyde (MDA) and nitric oxide products like nitrite (NO_2^-), nitrate (NO_3^-) and total nitrite (TNO_2^-) were significantly elevated, whereas enzymatic and non-enzymatic antioxidants were significantly lowered in cancer patients when compared to healthy subjects (231).

Progression—Reactive oxygen species have been much less well studied in regards to disease progression, likely because of the related difficulties in collecting appropriate materials for measurement and the influence of cancer treatment modalities on ROS generation and subsequent bi-products. Expression of nitrotyrosine and inducible nitric oxide synthase has, however, been associated with poor survival in stage III melanoma patients (232).

Prostaglandins, Cyclooxygenases, Lipoxygenases and Related Factors

Background

Prostaglandins (PGs) have a wide range of strong physiological effects and can be found in most tissues and organs (233). PGs constitute a group of lipid compounds that are enzymatically derived from essential fatty acids (EFAs) and have important functions in different cell types (234). EFAs are modified by either of two pathways: the prostaglandin H synthase-cyclooxygenase (COX) pathway or the lipoxygenase (ALOX) pathway. The COX

pathway produces thromboxane, prostacyclin and prostaglandins D, E & F. The COX pathway includes two rate-limiting enzymes, COX-1 & COX-2 (235). COX-1 has been traditionally characterized as constitutionally expressed and thus responsible for baseline PGs levels, while COX-2 is more easily inducible, including through IL-6 and peroxides. The ALOX pathway is inactive in leukocytes and synthesizes leukotrienes in macrophages (236). Both of these pathways, their intermediates or end products are involved in the inflammation response, although COX-2 has been given more attention in the investigation of cancer etiology in population-based research (235).

Measurement

The role of disruption in PG synthesis in cancer development can be evaluated at several points in the various pathways using several techniques. The most frequently used methods to measure levels of PGs in a variety of liquid biospecimens are chromatography-based methods, i.e. GC-MS, and antibody-based methods such as ELISAs and RIAs (237, 238). While GC-MS provides high sensitivity and specificity, the method also involves labor-intensive sample preparation and is not suitable for high throughput analysis. In contrast, antibody-based methods enable the measurements of multiple samples simultaneously; however, these assays frequently lack specificity (238). At present, the most precise, informative and reliable method, with a reasonable throughput is LC-MS/MS (239), which was recently optimized for the measurement of PGE_2 and PGD_2, by incorporating special standards in the samples (240). However, this approach is not high-throughput. COX-2 expression can also be measured by quantitative immunohistochemistry in tissue.

Cancer Associations

Etiology—Direct measurement of urinary PGE metabolites (PGE-M) has been associated with increased cancer risk for BC among postmenopausal women who did not regularly use non-steroidal anti-inflammatory drugs (NSAIDs) HR=2.1 (95% CI: 1.0-4.3); 2.0 (95% CI=1.0-3.9); and 2.2 (95% CI=1.1-4.3) for the second, third, and highest quartiles of PGE-M (241). Increasing quartiles of urinary PGE-M levels were also associated with risk of gastric cancer (statistically significant test for trend (P = 0.04)) (242).

Prognosis—A meta-analysis of 23 studies evaluating COX-2 expression from immunohistochemistry suggested that COX-2 over-expression in tumor tissues had an unfavorable impact on overall survival (OS) in CRC patients (HR=1.19, 95% CI=1.02-1.37) (243). COX-2 correlates with poor prognostic markers in BC (large tumor size and high tumor grade), but not with outcome (244) and with reduced survival in cervical and OC (245-247). In an investigation of COX-2 expression in bladder cancer, a weak association with recurrence in non-muscle invasive bladder tumors was observed (p-value = 0.048). In the multivariable analyses, COX2 expression did not independently predict any of the considered outcomes (248).

Transcription Factors and Growth Factors as Mediators of an Inflammation and Cancer Association

Background—Several substances created by the cellular mediators of inflammation propagate the inflammation response and their actions elicit a cellular growth response.

These growth factors/transcription factors are proteins that bind to cellular and nuclear receptors to elicit a downstream response. Nuclear factor-kappaB (NF-κB) one such transcription factor has been suggested to play a strong molecular role linking inflammation and cancer development (249, 250). NF-κB is activated downstream through 1) the toll-like receptor (TLR)-MYD88 pathway responsible for sensing microbes and tissue damage, as well as the inflammatory cytokines TNF-α and IL-1B (251). NF-κB activation can also be the result of cell-autonomous genetic alterations (252). NF-κB functions in inflammatory pathways by inducing the expression of inflammatory cytokines, adhesion molecules, cyclooxygenases, NO synthase and angiogenic factors, all propagating an exacerbated inflammation response (253). It also promotes tumor survival by inducing anti-apoptotic genes (*BCL2*) (254). A lack of checkpoint for growth factors such as NF-κB activation leads to increased proinflammatory cytokine and chemokine secretion as well prostaglandin release downstream of NF-κB signaling which were shown to promote neoplasia (255).

Another transcription factor also believed to play a pivotal role in linking inflammation and cytokines to cancer development and progression is STAT3. Most inflammatory signals affect tumorigenesis by activating STAT3 in a similar method to those described for NF-κB (256, 257). Persistent STAT3 activation in malignant cells stimulates proliferation, survival, angiogenesis, invasion and tumor-promoting inflammation (258, 259).

Measurement—Transcription factors such as NF-κB activity can be measured on various levels including: 1) quantity in fluids 2) levels of activation and 3) translocation. Quantification can be completed using ELISA and other high sensitivity assays; however, stability in blood samples is an issue. Levels of NF-κB activation in stimulated normal peripheral blood lymphocytes can be completed using a real-time PCR to measure of Iκβα mRNA levels as a rapid, sensitive, and powerful method to quantify the transcriptional power of NF-κB. It can be used for clinical evaluation of NF-κB status, but requires cell culture and is thus not easily adaptable in epidemiologic studies (260). NF-κB translocation to the nucleus, where it regulates cytokine and immunoglobulin expression, can be measured by both confocal microscopy and flow cytometry (261).

Cancer Associations—In comparison to the other markers discussed in this review, comparatively fewer studies directly quantifying cancer risk and prognosis related to changes in NF-κB and STAT3 quantity in fluids, levels of activation and translocation have been completed, perhaps due to the difficulty of appropriate biospecimen collection. Several investigations have examined polymorphisms in NF-κB genes in the development of OC (262) and CRC (263, 264). Examination of NF-κB activation has suggested an association with a high-risk subset of hormone-dependent BC (263) with increased expansion of cancer stem cells in basal-like BCs (265). Results also suggest that NF-κB activation maybe be predictive of response to treatment (266) and survival (267) in CRC. Proteasome inhibitors used for treatment of various cancers including multiple myeloma and NHL (268) elicit their effects partially reducing NF-κB activity (269).

DISCUSSION

The Potential for Prevention and Therapeutic Intervention

Prevention—Several of the biomarkers discussed in this review presently have the potential to be used for cancer prevention. From a primary and tertiary prevention perspective, the use of non-steroidal anti-inflammatory drugs has been related to reduced cancer risk at several sites including BC, CRC, OC, GC and LC (270-276) and improved disease outcomes (277). These data suggest that blocking inflammatory pathways, in this case the prostaglandin-related and subsequent downstream pathways (278) can prevent the development of cancer at the population level. Evaluations of whether intervention at different points across the inflammation spectrum can prevent cancer are an interesting area of developing research (279-281) that could yield great impact in the prevention of cancer.

From a secondary prevention perspective, several research groups have and continue to evaluate the utility of inflammatory biomarkers in the development of risk prediction models. For example, Pine et al. observed that 10-year predicted risk for LC was highest among those smokers with elevated CRP and IL-8 in the PLCO study (54). Extensions of these methods and models with other types of inflammatory markers and other cancer sites may help to identify those at greatest risk for developing cancer, and therefore refine the population that would most benefit from increased screening based on their inflammatory profiles.

Therapeutic intervention—Several developing avenues of immune based therapies including tumor vaccine approaches, immune-checkpoint inhibitors and antagonists of immunosuppressive molecules such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) among others which seem promising in early stages of development and trials (282). This topic is beyond the scope of this review, but it is a rapidly emerging area in cancer therapeutics and early results appear quite promising with cancer immunotherapy heralded as the scientific breakthrough of 2013 (283).

The Need for Integrative Targeted Approaches to Examine Inflammation in Cancer

As the inflammation response and its role in carcinogenesis is vastly complex in nature, novel approaches to characterize the roles of inflammatory markers in cancer development and progression to identify elevated risk profiles and subsequent intervention targets are needed. An approach limited to single markers will yield ineffective and fragmented results suboptimal for the reduction of cancer burden. Three overarching principles should be the goal of future research in this area.

First, investigations should aim to be as comprehensive as possible in order to examine multiple exposures as well as their interactions (Figure 1). For example, assessing a comprehensive set of biomarkers will provide a better picture and will enable more-pathway-based analyses. In addition, evaluating germ-line variation, epigenetic modification, expression and protein product levels in a comprehensive pathway-based analytic approach would provide a more resolute image of the relevant associations. This will, however, require substantial funding and access to a diverse set of biospecimens.

Second, the use of existing data platforms, such as large prospective studies and bio-repositories should be targeted for the evaluation of these integrative hypotheses to be able to better address the issue of causality. This approach will require focusing on analytes that are less sensitive to degradation over time. Integration with lifestyle factors in these data platform would be also important as several of them (per Introduction) are correlated with the inflammatory markers of interest. Mediation analyses or structural equation modeling/ path analyses may be necessary to adequately unravel the complex associations of interest.

Lastly, etiologic and prognostic associations should be evaluated across cancer sites where possible. As discussed, imbalances in the markers of altered inflammation have been associated differently with cancers at multiple sites, yet it is clear that inflammatory imbalances play a role to some degree across the majority of solid tumor sites. Comprehensively evaluating associations similarly across cancer sites where sample availability permits, for example in a large cohort setting, dramatically increases the potential benefit of identifying chemopreventive or therapeutic targets. Several initiatives are underway to advance this cross-cancer inflammation hypothesis, yet more research is needed.

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Cancer Site Abbreviations

LC	Lung Cancer
CRC	Colorectal Cancer
BC	Breast Cancer
PC	Prostate Cancer
EC	Endometrial Cancer
NHL	Non-Hodgkin's Lymphoma
RCC	Renal Cell Carcinoma
OC	Ovarian Cancer
CLL	Chronic Lymphocytic Leukemia
ESOC	Esophageal Cancer
HCC	Hepatocellular Carcinoma
BLC	Bladder Cancer

PANCC	Pancreatic Cancer
GC	Gastric Cancer

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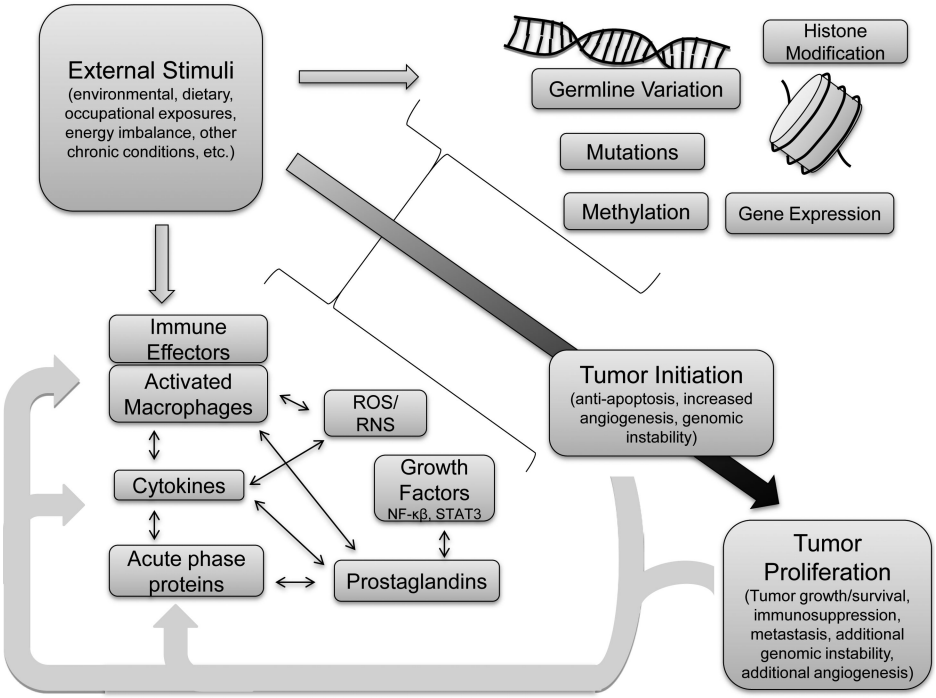

Figure 1.

The complex interactions involved in the role of inflammation in the cancer progression spectrum.

Table 1

Summary of inflammatory markers, associated techniques, tissue requirements with corresponding advantages and disadvantages of their application.

Inflammatory Marker	Explanation	Techniques*	Advantages	Disadvantages	Tissue Requirement**	Current Evidence of Cancer Association***
Cytokines and Chemokines						
Cytokines/ Chemokines	Small secreted proteins which mediate as well as regulate immunity, inflammation, and hematopoiesis. Cytokines generally act at very low concentrations over short distances and short time spans.	ELISA, multiplex bead assays	Simultaneous measurement of several cytokines possible	No strong evidence to predict progression or survival. Blood draw and processing conditions can affect levels. Degradation over time when samples stored improperly or over multiple freeze/thaw cycles. Costly Tumors create an inflammatory milieu and can produce cytokines. Difficult to assess reverse causality without longitudinal data. Lack of standardization of assays Function in multiple pathways (lack of specificity)	Serum/plasma/tissue/ cell culture supernatant Depends on assay used (5-100uL)	Direct measurement in several cancers with correlation with tumor stage and disease extent. Related to cancer risk in prospective collected data.
Immune-Related Effectors						
White cell count	A measure of the total white blood content, generally indicative of infection (neutrophils and monocytes- bacteria, lymphocytes - viral, eosinophils - parasitic).	FACS	Routinely measured and used in clinical practice (useful for prediction and maximization of currently available data and employed clinical algorithms). Stable over time when frozen. Blood neutrophilia and thrombocytosis established as indicators of systemic inflammatory response.	Levels may be altered due to transient infection not-related to chronic inflammation.	Serum Portable kits available that need only 10uL	Associated with lung cancer risk in prospectively collected data. Associated with cancer-related mortality in prospective studies.

Inflammatory Marker	Explanation	Techniques*	Advantages	Disadvantages	Tissue Requirement**	Current Evidence of Cancer Association***
Glasgow Prognostic score	A combination of Albumin and C-reactive protein measurements into a 3 level predictive score. 2 when both C-RP>10mgl-1 and albumin <35gl-1. 1 if only one abnormality present. 0 if both not.	Combined C-RP and albumin tests.	Inexpensive if C-RP and albumin already measured. Standardized score	Levels may be altered due to transient infection not-related to chronic inflammation same issues for C-RP.	Serum	Not related to risk of cancer development. Evidence suggests use as a prognostic score independent of tumor stage and treatment.
Neutrophil/Lymphocyte ratio	The ratio of neutrophils to lymphocytes, where higher values reflect states of dramatic inflammation.	Same as white cell count	Potential as a simple, cost effective, and readily available test.	Different cutoff levels reported across studies. Additional value obtained beyond normal white cell counts is of question.	Serum	Shown to be related to survival in many cancer sites after diagnosis and various treatment modalities.
Platelet/Lymphocyte ratio Th17 lymphocytes	The ratio of platelets to lymphocytes, where higher values reflect states of dramatic inflammation. Recently discovered inflammatory T-cell subset with associations to autoimmune diseases and potential role in cancer risk and progression.	Same as white cell count IHC, FACS	Routinely measured and used in clinical practice (useful for prediction and maximization of currently available data and employed clinical algorithms). Potential as a simple, cost-effective, and readily available test. All three cell types give insight into the T-cell functional status and thus immune responses. A combined analysis can potentially advance the current analysis focusing on one of the cell types.	Levels may be altered due to transient infection not-related to chronic inflammation. Not well studied with risk of disease. Heterogeneous results are assumable between cancer entities. Material acquisition might be problematic.	Serum Tissue (TMAs), Peripheral blood cells (requires fresh cells for FC)	Predicts outcomes in colorectal cancer. Not as of yet extensively studied with risk.
Acute Phase Proteins						
C-reactive Protein	An acute phase protein produced by hepatocytes in response to pro-inflammatory cytokines. Produced in times of inflammation to age damaged cells for excretion by the liver.	Fluorescence polarization-immunoassay, Nephelometry, ELISA	Quantitative and sensitive measurement	Non-specific marker of inflammation	Serum or plasma	Large meta-analysis indicates poor evidence to support use as a diagnostic marker; may be useful in

Inflammatory Marker	Explanation	Techniques*	Advantages	Disadvantages	Tissue Requirement**	Current Evidence of Cancer Association***
						colorectal and lung cancer; colorectal and lung cancer
			Easily measured	Levels may be altered due to transient infection not-related to chronic inflammation (CRP rises drastically in acute inflammation, such as infection, therefore several measurements over time are encourage for a better characterization of chronic states.		
Serum Amyloid A (SAA)	Similar to CRP an acute phase protein, but levels may be even more responsive to inflammation.	Fluorescence polarization-immunoassay, Nephelometry, ELISA	Easily measured Rather novel marker	Limited evidence for use to predict treatment response.	Serum or plasma	Strongly associated with worse long-term survival from breast cancer.
Reactive Oxygen & Nitrogen Species						
Reactive Oxygen & Nitrogen Species	Chemically-reactive molecules produced as by-products of normal metabolic processes in all aerobic organisms. Characterized by the presence of unpaired electrons.		Would provide a direct estimate of ROS burden and would be beneficial for prediction of risk and carcinogenicity of lifestyle patterns.	No standardized methods to capture actual ROS levels in humans to date Compounds have very short half-life in systems. Questionable quality due to the volatility of compounds. Levels affected by lifestyle factors i.e. Nutritional status	Tissue Serum	Direct evidence and measurement in prospective studies lacking Signaling Pathways regulated by ROS in cancer models. Association with expression/enzyme activity of ROS/RNS producers shown in various cancers. Weak evidence of variants in ROS/RNS production genes and cancer risk.
Oxidatively/Nitrosatively modified DNA, or proteins	The product of excess ROS/RNS in tissue					
3-Nitrotyrosine	The product of nitrosylated proteins	HPLC		Not well standardized	Healthy or tumor tissue	Higher level observed in the tumors of never smoking lung cancer cases suggesting a

Inflammatory Marker	Explanation	Techniques*	Advantages	Disadvantages	Tissue Requirement**	Current Evidence of Cancer Association***
						marker for inflammation-related carcinog marker for inflammation-related carcinog marker for inflammation-related carcinog marker for inflammation-related carcinog
8-hydroxy-2′-deoxyguanosine (8-oxodg or 8-OHdG)	8-oxodG is a sensitive surrogate biomarker for in vivo oxidative stress.	ELISA, HPLC methods	Provides a measure of DNA damage due to ROS.	Not tissue specific	Plasma, Urine	Elevated levels observed in several cancers included esophageal, colon and breast
8-Iso-PGF_{2_α}	Lipid peroxidation product.	ELISA, HPLC methods	Provides a measure of DNA damage due to ROS.	Not tissue specific	Plasma, Urine	Related to breast and colon cancer risk
Malondialdehyde(MDA)	Lipid peroxidation product.	ELISA, HPLC methods	Provides a measure of DNA damage due to ROS.	Not tissue specific	Plasma, Urine	Associated with lung and colon cancer risk
Trans-4-hydroxy-2-noneal (HNE)	Lipid peroxidation product.	ELISA, HPLC methods	Provides a measure of DNA damage due to ROS.	Not tissue specific	Plasma, Urine	Not as well studied as other peroxidation products
Prostaglandins, Cyclooxygenases, Lipoxygenases and Related Factors						
Prostaglandin levels	Lipid compounds containing 20 carbon ring including a 5-carbon group. Produced by the sequential oxidation of Prost. By COX-1 &2. COX-1 is believed to control baseline levels of prosts, while COX-2 increases levels of PGE by response to stimulation	ELISA Liquid chromatography/ tandem mass spectrometry		Levels may be tissue-specific difficult to measure. Affected by several pharmacologic interventions which could complicate association modeling. Some prostaglandins are rapidly degraded	Saliva, Urine, Serum, EDTA and Heparin Plasma	
COX-2 Expression	Enzymes integral to prostaglandin synthesis.	IHC	Interest as target for chemo-prevention	Levels may be tissue-specific difficult to measure. Affected by several pharmacologic interventions which could complicate association modeling.	Tissue Culture Media TMA	COX-2 expression observed in nearly every tumor type examined.
Transcription Factors and Growth Factors						
NF-κB Activation	A transcription factor that functions in inflammatory pathways by inducing the	ELISA RtPCR to measure mRNA	Can measure quantity, activation,	Clinical evaluation of NF-κB requires cell culture.	Serum, plasma, peripheral blood lymphocytes	Predictive of outcomes in BC and CRC.

Inflammatory Marker	Explanation	Techniques*	Advantages	Disadvantages	Tissue Requirement**	Current Evidence of Cancer Association***
	expression of inflammatory cytokines, adhesion molecules, cyclooxygenases, and expression of inflammatory cytokines, adhesion molecules, cyclooxygenases, expression of inflammatory cytokines, adhesion molecules, cyclooxygenases, expression of inflammatory cytokines, adhesion molecules, cyclooxygenases,		cyclooxygenases, NO synthase and angiogenic factors. cyclooxygenases, NO synthase and angiogenic factors. cyclooxygenases, NO synthase and angiogenic factors. cyclooxygenases, NO synthase and angiogenic factors.			
STAT3 Activation	A transcription factor activated in response to various factors including inflammatory cytokines. Mediates the expression of several key cell growth and apoptosis genes.	ELISA		Also regulated by other non-inflammatory growth factors.	Serum or plasma	Less well studied than NF-κB.

* Most commonly cited techniques although others may exist

** Quantity of sample will depend on quality of material extraction, processing and type

*** For additional details see text