

Nutritional and Botanical Modulation of the Inflammatory Cascade—Eicosanoids, Cyclooxygenases, and Lipoxygenases—As an Adjunct in Cancer Therapy

Jeanne M. Wallace, PhD, CNC

Emerging on the horizon in cancer therapy is an expansion of the scope of treatment beyond cytotoxic approaches to include molecular management of cancer physiopathology. The goal in these integrative approaches, which extends beyond eradicating the affected cells, is to control the cancer phenotype. One key new approach appears to be modulation of the inflammatory cascade, as research is expanding that links cancer initiation, promotion, progression, angiogenesis, and metastasis to inflammatory events. This article presents a literature review of the emerging relationship between neoplasia and inflammatory eicosanoids (PGE₂ and related prostaglandins), with a focus on how inhibition of their synthesizing oxidases, particularly cyclooxygenase (COX), offers anticancer actions *in vitro* and *in vivo*. Although a majority of this research emphasizes the pharmaceutical applications of nonsteroidal anti-inflammatory drugs and selective COX-2 inhibitors, these agents fail to address alternate pathways available for the synthesis of proinflammatory eicosanoids. Evidence is presented that suggests the inhibition of lipoxygenase and its by-products—LTB₄, 5-HETE, and 12-HETE—represents an overlooked but crucial component in complementary cancer therapies. Based on the hypothesis that natural agents capable of modulating both lipoxygenase and COX may advance the efficacy of cancer therapy, an overview and discussion is presented of dietary modifications and selected nutritional and botanical agents (notably, omega-3 fatty acids, antioxidants, boswellia, bromelain, curcumin, and quercetin) that favorably influence eicosanoid production.

The molecular management of cancer physiopathology is a promising focus for integrative cancer therapies. In addition to eradicating malignant cells, the expanded goal in integrative medicine is to control the cancer phenotype, and thereby to improve the quality of life and extend the survival of cancer patients. Therapeutic approaches employing this paradigm strive to optimize host nutritional and metabolic status (which affect genetic stability and gene expression), control tumor-promoting messenger molecules (such as growth factors and hormones), promote differentiation and

apoptosis, curtail angiogenesis, deter invasion and metastasis, and bolster immune surveillance and tumor immunoreactivity.¹ A key strategy in this model, which may affect several of these targets, appears to be the modulation of inflammatory eicosanoids.

Eicosanoids are hormone-like compounds with local activity, produced both by tissue cells and by tumor-infiltrating leukocytes. They are synthesized from polyunsaturated fatty acids, predominately arachidonic acid. Collectively, eicosanoids have potent biological activities in cell proliferation and tissue repair, blood clotting, blood vessel permeability, inflammation, and immune cell behavior.² Prostaglandins are a well-known class of eicosanoid, and prostaglandins in the 2 series (e.g., PGE₂) have proinflammatory activities.

Prostaglandins are synthesized by the action of prostaglandin synthase enzymes, also known as cyclooxygenases (COXs). Two distinct isoforms of COX have been discovered, COX-1 and COX-2. COX-1 is constitutively expressed and is cytoprotective. It is required for normal “housekeeping” functions, such as protection of gastrointestinal mucosa, maintenance of renal function, and platelet stabilization and activity.³ A second isoform of COX, COX-2, is inducible and expressed primarily following inflammatory insult. COX-2 synthesizes series-2 prostaglandins (e.g., PGE₂, PGF₂-α) that contribute to pain, inflammation, and swelling. COX-2 can be stimulated by inflammatory mediators, cytokines, growth factors, and tumor promoters. COX-2 is inhibited by steroids and nonsteroidal anti-inflammatory drugs (NSAIDs). A detailed explanation of the biochemical pathways of these and additional eicosanoid compounds is presented later in this article, following a literature review of the role of COX-2 and its byproducts in neoplastic diseases.

JMW is at Nutritional Solutions, Inc., North Logan, Utah.

Correspondence: Jeanne M. Wallace, Nutritional Solutions, Inc., 2935 North, 1000 East, North Logan, UT 84341, USA. E-mail: BTnutrition@aol.com.

COX-2 and PGE2 in Cancer: Review of the Literature

There is a large body of literature, dating back to 1974,⁴ exploring the connection between prostaglandins and cancer. Early research established that human and experimental tumors have elevated amounts of E series prostaglandins and that NSAID blockade of prostaglandin synthesis inhibits tumor growth *in vitro* and *in vivo*.⁵ The development of selective COX-2 inhibitors, celecoxib and rofecoxib, and the prospect of their therapeutic application in chemoprevention and cancer therapy, has fueled an explosion of research on the role of inflammatory modulation in cancer. The following discussion provides a review, for selected types of cancer, of the recent literature on this topic. The studies reviewed here are a small but representative sample of the published scientific literature from 1995 through 2001. A summary of this research is presented in Table 1.

Colon Cancer

The relationship between COX-2 and cancer was initially discovered, and has been most fully explored, in colon cancer. Research initially focused on chemoprevention. Ample epidemiologic evidence supports the chemopreventive effect of NSAIDs (especially aspirin) on both polyp formation and the risk of colorectal cancer, with some studies reporting as high as a 40% to 50% reduction in cancer mortality.^{6,11} Chemopreventive studies on selective COX-2 inhibitors have also demonstrated positive effects.¹²⁻¹⁴

In vivo studies show similar chemopreventive effects; for example, long-term (40-week) administration of a selective COX-2 inhibitor in rats reduces the incidence of azoxymethane-induced colon neoplasms from 80% to 85% in the control group and from 45% to 50% in the treatment group.¹⁵ Some of the strongest evidence implicating COX-2 in colorectal tumorigenesis derives from research on mice with multiple intestinal neoplasia (Min mice), who harbor a mutation in the tumor suppressor gene and are predisposed to multiple intestinal adenoma (forming up to 800 polyps) and subsequent colon cancer. Feeding COX-2 inhibitors to Min mice dramatically suppresses tumor growth.¹⁶ When Min mice are crossbred with COX-2 knockout mice, their progeny develop markedly reduced numbers of tumors.¹⁶⁻¹⁸

Controlled trials of patients with familial adenomatous polyposis (FAP) have achieved 30% reductions in polyp burden (size and number) with daily administration of celecoxib.^{19,20} Because a variety of doses have been used in human studies to date, further research is needed to clarify the dose that safely confers optimum chemopreventive effects. Identification of at-

risk individuals who may most benefit from this chemopreventive strategy is yet to be characterized, excepting those with FAP. The Food and Drug Administration (FDA) approved celecoxib for use as an adjunct treatment for FAP in December 1999. Considering the toxicity of chronic NSAID use, and the potential although as yet not fully documented side effects of selective COX-2 inhibitors, the benefit-to-risk ratio needs to be determined. Consequently, blanket recommendation of COX inhibitors for colon cancer prevention is premature. For this reason, much research has turned its focus to the application of COX inhibition in cancer treatment beginning with studies to characterize the up-regulation of COX-2 in cancer and its biological effects.

COX-2 protein overexpression is demonstrated in more than 80% of human colorectal adenoma and carcinoma biopsy specimens, but it is absent in adjacent histologically normal tissue.^{21,22} Levels of PGE2 are also significantly elevated in colon cancer samples as compared to histologically normal mucosa.²³

Administration of NSAIDs or selective COX-2 inhibitors has growth-suppressive effects both *in vitro* and *in vivo*. NSAIDs (aspirin, indomethacin, naproxen, and piroxicam) reduce the proliferation of HT-29 colon adenocarcinoma cells *in vitro* via cell cycle arrest—increasing the proportion of cells in G₀/G₁ phase and reducing the proportion of cells in G₂/M and S phases—and programmed cell death.²⁴ Xenografts of HCA-7 colon cancer cells (which express high levels of COX-2) in nude mice sustain an 85% to 90% growth suppression with daily administration of celecoxib compared to no growth inhibition in the placebo group.²² An interesting relationship has been documented between the activities of COX-2 and butyrate, a short-chain fatty acid derived from bacterial fermentation of dietary fibers. Butyrate is known to induce differentiation and apoptosis in colorectal tumor cells *in vitro*. HT-29 colon carcinoma cells can be sensitized to the growth-inhibitory effects of butyrate by a selective COX-2 inhibitor, methanesulfonamide (NS-398).²⁵ In this study, treatment of the cell line with NS-398 alone did not achieve detectable growth inhibition, and cell lines not expressing COX-2, as determined by PGE2 production, were not sensitized to butyrate. Further research is indicated to examine the potential interdependence of butyrate and COX-2 inhibition. If *in vivo* research confirms the relationship, it could explain the lack of consistency in research on butyrate and offer a means to increase the therapeutic efficacy of strategies to boost butyrate levels.

Increased COX-2 expression in tumor specimens from colorectal carcinoma patients is significantly correlated with unfavorable clinicopathological characteristics—such as tumor size and Dukes' staging,

Table 1. Selected Research Findings for Cyclooxygenase-2 (COX-2) and PGE-2 in Cancer

Brain tumors	
Shono et al. (2001)	COX-2 overexpression in brain tumor tissue is associated with clinically more aggressive gliomas and is the strongest predictor of outcome for glioma patients, independent of all other variables ³¹
Joki et al. (2000)	Although present in all brain specimens sampled, COX-2 protein expression is significantly higher in tumor than normal brain, and considerably higher in high-grade than in low-grade gliomas; NS-398 inhibits growth of 3 human glioma cell lines in vitro in a dose-dependent manner ²⁹
Tatsuhiko et al. (2000)	Significant positive correlation between COX-2 staining and tumor grade in glioma samples; NS-398 reduces cell proliferation and migration and induces apoptosis in vitro ³⁰
Petersen et al. (2000)	Selective COX-2 inhibition decreased cell survival, induced apoptosis, and slowed tumor growth in vitro and in vivo in human glioma cell line U251 ³²
Breast cancer	
Blumenthal et al. (2001)	Celebrex® has impressive in vitro growth inhibition on breast cancer cell lines ³⁸
Kundu et al. (2001)	Elevated PGE2 confers increased metastatic potential in a murine model of breast cancer ⁴²
Koki et al. (2001)	In 25 women with breast cancer, COX-2 overexpressed in 80% of HER-2/neu positive tumors ⁴⁵
Harris et al. (2000)	Treatment with selective COX-2 inhibitor reduced the incidence of experimentally induced breast cancers in lab animals in vivo ³⁷
Harris et al. (1999)	Prospective cohort study shows breast cancer rates declined by about 50% among those with regular ibuprofen intake ³³
Gilhooly and Rose (1999)	Modest breast cancer chemopreventive for selective COX-2 inhibitors ³⁵
Fischer et al. (1999)	In 341 women with invasive breast carcinoma, regular nonsteroidal anti-inflammatory drug (NSAID) ingestion was inversely associated with size of primary tumor, lymph node status, and number of involved axillary nodes ⁴⁰
Hwang et al. (1998)	Modest chemopreventive role for COX-2 inhibitors in breast cancer ³⁶
Harris et al. (1996)	Up to 40% reduction in risk of developing breast cancer among women who regularly use NSAIDs, 3 to 7 times a week for 1 to 5+ years ³⁴
Liu and Rose (1996)	Highly invasive MDA-MB-231 breast cancer cell line has high COX-2 expression (and high PGE2 production) compared to a less invasive cell line ⁴¹
Colorectal cancer	
Masunaga et al. (2000)	Increased COX-2 expression correlates with tumor size, differentiation, vascularization, number of metastatic lymph nodes, and Dukes' stage; patients with COX-2 positive tumors have significantly shorter survival times ²⁶
Tomozawa et al. (2000)	High COX-2 expression significantly correlated with tumor recurrence and metastasis ²⁸
Hao et al. (2000)	COX-2 overexpression found in more than 80% of adenoma and carcinoma tissue ²¹
Crew et al. (2000)	COX-2 inhibitor sensitizes HT-29 colon carcinoma cells to the growth-inhibitory effects of butyrate ²⁵
Sheehan et al. (1999)	Elevated COX-2 staining in colorectal cancer patients is correlated with advanced disease and poorer prognosis ²⁷
Smalley et al. (1999)	Up to 50% decrease in colorectal carcinoma mortality among aspirin or NSAID users ⁸
Kawamori et al. (1998)	Celecoxib exerts chemopreventive activity against colon carcinogenesis ¹²
Fukutake et al. (1998)	COX-2 inhibitor exerts chemopreventive effect in mice ¹⁴
Hara et al. (1997)	Selective COX-2 inhibitor induces apoptosis in human colorectal cancer cell lines ¹³
Sheng et al. (1997)	COX-2 overexpressed in mucosa of colorectal cancer patients but minimally expressed in normal colonic epithelium ²²
Sheng et al. (1997)	Compared to placebo, celecoxib suppresses growth of tumor xenografts by 85% to 90% in nude mice ²²
Shiff et al. (1996)	NSAIDs reduce proliferation of HT-29 colon cancer cells in vitro via cell cycle arrest and apoptosis ²⁴
Thun (1996)	Decreased risk of gastrointestinal cancers in NSAID users ⁹
Oshima et al. (1996)	COX-2 null mice have significant decrease in number of polyps ¹⁸
Rigas et al. (1993)	Biopsy samples of human colon cancer tissue contain significantly elevated levels of PGE2 compared to normal tissue samples from the same patients ²³
Gastric cancer	
Kang et al. (2001)	Overexpression of COX-2 observed in patients' tumor tissues; aspirin reduces PGE2 production by 50% after 24-hour exposure in vitro; selective COX-2 inhibitors induce apoptosis in gastric cancer cell line SNU-216 ⁴⁹
Ohno et al. (2001)	COX-2 indices significantly higher in gastric carcinoma with deep invasion ⁵¹
Chen et al. (2001)	Patients with COX-2-positive gastric adenocarcinoma have poorer prognosis than those with COX-2-negative tumors ⁵⁴
Lim et al. (2000)	Up-regulation of COX-2 in gastric cancer tissues (from 104 surgically resected gastric adenocarcinoma patients) compared to normal paired mucosa, but no correlation between clinicopathological characteristics of gastric cancer patients and intensity of COX-2 expression ⁵²
Uefuji et al. (2000)	COX-2 protein overexpressed in 74% of gastric cancers and intensity of COX-2 expression significantly correlated with lymph node involvement ⁵³
Ratnasinghe et al. (1999)	COX-2 is overexpressed in gastric adenocarcinoma ⁵⁰
Sawaoka et al. (1998)	Selective and nonselective COX inhibitors suppress cell proliferation in gastric cancer cell lines that express COX-2 in vitro ⁴⁸
Gynecological cancer	
Kulkarni et al. (2001)	COX-2 detected in 12 of 13 cases of cervical cancer but undetectable in normal cervical tissue ⁵⁶
Sales et al. (2001)	COX-2, PGE2 synthesis, and expression of PGE2 receptors are up-regulated in malignant tissue of the uterine cervix but not in normal cervix ⁵⁵
Gaffney et al. (2001)	Increased COX-2 expression significantly correlates with diminished survival and disease-free survival in patients with invasive carcinoma of the cervix treated with radiotherapy ³⁹

(continued)

Table 1. Continued

Comerci et al. (2001)	Staining intensity of COX-2 significantly greater in endometrial hyperplasia and carcinoma compared to normal endometrium ⁵⁷
Ryu et al. (2000)	COX-2 expression observed in all surgical samples of 36 patients with cervical cancer and was significantly elevated in those with lymph node or parametrial involvement; COX-2 expression significantly stronger at the tumor invasion site ⁵⁸
Head and neck cancer	
Gallo et al. (2001)	COX-2 higher in tumor samples of squamous cell carcinoma of the head and neck (HNSCC) patients than in normal mucosa, and COX-2 protein expression correlated with tumor vascularization, vascular endothelial growth factor expression in tumor tissue, and lymph node metastasis ⁵¹
Sumitani et al. (2001)	Selective COX-2 inhibition suppressed proliferation of squamous cell oral carcinoma cell line in vitro; addition of PGE2 reversed this effect ⁶³
Nishimura et al. (1999)	COX-2 inhibitor suppresses growth in human head and neck squamous carcinoma xenografts ⁶²
Mestre et al. (1999)	Nearly 100-fold increase in COX-2 mRNA detected in HNSCC, and COX-2 protein detected in 6 of 6 cases of HNSCC but undetectable in normal mucosa ⁶⁰
Lung cancer	
Williams et al. (2000)	Significantly reduced tumor growth in COX-2 null mice grafted with Lewis lung carcinoma; tumors grown in COX-2 null mice have decreased vascular density ⁶⁷
Hosomi et al. (2000)	COX-2 overexpression detected in more than 80% of precursor lesions of human lung adenocarcinoma ⁶⁴
Ochiai et al. (1999)	COX-2 expression in non-small cell lung cancer significantly higher than in normal lung tissue, and significantly higher in adenocarcinoma than in squamous cell carcinoma autopsy samples ⁶⁸
Watkins et al. (1999)	COX-2 highest in adenocarcinoma cells and lower in large cell and squamous cell carcinoma, respectively; COX-1 undetected ⁶⁵
Achiwa et al. (1999)	Presence of COX-2 in human lung associated with poorer prognosis in stage I lung cancer patients ⁶⁹
Pancreatic cancer	
Kokawa et al. (2001)	Inhibitory effect of aspirin on 4 pancreatic cell lines parallels their level of COX-2 expression ⁷⁴
Yip-Schneider et al. (2000)	COX-2 expression significantly higher in pancreatic tumor than in matched normal adjacent tissue; COX inhibitors inhibit cell growth in pancreatic tumor cell lines, with greater inhibitory effect for cell lines with stronger COX-2 expression ⁷³
Tucker et al. (1999)	COX-2 mRNA increased >60-fold in pancreatic cancer tissue compared to adjacent nontumorous tissue ⁷⁰
Koshiba et al. (1999)	COX-2 expression identified in all pancreatic cancer tissues tested and in 60% of 5 pancreatic cancer cell lines; no significant correlation between COX-2 expression and prognosis or clinicopathological factors in this study ⁷¹
Okami et al. (1999)	Moderate to strong overexpression of COX-2 found in 90% of pancreatic carcinomas compared to no or weak expression of COX-2 in benign tumors ⁷²
Prostate cancer	
Subbarayan et al. (2001)	Up-regulation of COX-2 and PGE2 is correlated with decreased apoptosis in PC-3, LNCaP, and DU145 prostate cancer cell lines ⁷⁸
Gupta et al. (2000)	3.4-fold increase in mean levels of COX-2 mRNA in prostate cancer tissue compared to benign tissue from same patient ⁸⁰
Fischer et al. (2000)	Significant risk reduction for prostate cancer among NSAID users ⁷⁵
Liu et al. (2000)	COX-2 inhibition suppresses PC-3 cell tumor growth in vivo ⁷⁹
Irani et al. (1999)	Patients with increased peritumoral inflammation have significantly more postoperative biochemical recurrence than those with low inflammation ⁸¹
Tjandrawinata and Hughes-Fulford (1997)	Administration of exogenous PGE2 increases cell proliferation of PC-3 cell lines and up-regulates COX-2 expression ⁷⁷
Urinary bladder cancer	
Ristimaki et al. (2001)	COX-2 highly expressed in bladder carcinomas with highest expression of invasive tumors associated with invading cells ⁸⁴
Shirahama (2000)	COX-2 expression undetected in normal urothelial samples but increased in tumors and significantly correlated to tumor stage in muscle-invasive tumors ⁸³
Khan et al. (2000)	No detection of COX-2 in normal urinary bladder epithelium of canines, but increased COX-2 expression in neoplastic epithelium in primary tumors and in metastatic lesions ⁸²
Komhoff et al. (2000)	Elevated expression of COX-2 demonstrated in a high percentage of high-grade bladder carcinomas ⁸⁶
Kitayama et al. (1999)	Dose-dependent reduction in nitrosamine-induced bladder tumors in animals with COX-2 inhibitor nimesulide ⁸⁶
Ziegler (1999)	Celecoxib chemoprevention of nitrosamine-induced bladder tumors in vivo ⁸⁷
Okajima et al. (1998)	Chemoprevention of rat urinary bladder cancer with COX-2 inhibitor ⁸⁵

differentiation, lymph node involvement, vascularization, and metastases—and is associated with significantly shorter survival time compared to patients

with COX-2 negative tumors.^{26,27} In addition, COX-2 overexpression is correlated with recurrence of colorectal cancer.²⁸

Brain Cancer

COX-2 is constitutively expressed in normal brain tissue. Nonetheless, comparative evaluations of COX-2 expression in human glioma tumors and normal brain samples show that COX-2 expression is significantly higher in tumor and that COX-2 expression is significantly higher in high-grade glioma than in low-grade glioma.^{29,30} Recent work at the University of Texas, M. D. Anderson Cancer Center confirms that elevated COX-2 expression in brain tumors is associated with clinically more aggressive gliomas and is a strong predictor of poor survival, particularly for patients with glioblastoma multiforme.³¹ Immunohistochemistry evaluations of tumor specimens from 66 patients found that high COX-2 expression (>50% of cells staining positive) was the strongest predictor of outcome, independent of all other variables.

In vitro application of selective COX-2 inhibitors has been shown to reduce proliferation of human glioma cell lines, impede tumor cell migration, and increase the number of apoptotic cells.^{29,30} COX-2 inhibition also slows tumor growth rate in vivo in glioma murine xenografts.³²

Collectively, these findings strongly suggest a potential role for COX-2 inhibitors as an adjunctive therapy for brain tumors.

Breast Cancer

The frontier of COX inhibition in breast cancer prevention and treatment is being probed by several lines of evidence. Epidemiologic research demonstrates a 40% to 50% decrease in the risk of breast cancer among women who are chronic users of NSAIDs.^{33,34} The risk reduction is similar to that reported for colon cancer chemoprevention.⁸ A modest chemopreventive role for selective COX-2 inhibitors has also been reported in breast cancer.^{35,36} Significant chemoprevention of chemically induced breast cancer in lab rats can be achieved by treatment with ibuprofen or celecoxib.³⁷

In vitro analyses have demonstrated an IC₅₀ for celecoxib in 12 solid tumor lines ranging from 28 to 58 μ M, with impressive growth inhibition on breast cancer cell lines.³⁸ At very high doses, celecoxib (1500 mg/kg/day) has significant in vivo antineoplastic activity, achieving tumor regressions in 90% of tumor-bearing animals treated for 6 weeks.³⁹ The excessive doses employed in this study limit the relevance of its finding in clinical practice.

A retrospective analysis of 341 women with invasive breast carcinoma found regular prior NSAID ingestion was inversely associated with the size of the primary tumor, lymph node metastasis, and the number of involved axillary nodes,⁴⁰ suggesting NSAID use may impact favorably on factors that determine prognosis and clinical outcome of women with breast cancer.

The supposition that COX-2 is implicated in breast cancer invasion is supported by the observation that the highly invasive, metastatic MDA-MB-231 cell line shows high COX-2 mRNA and protein and elevated PGE₂ production, whereas less invasive cell lines have lower COX-2 expression.⁴¹ In a murine model of metastatic breast cancer, PGE₂ levels are positively correlated with increased tumorigenic and metastatic potential.⁴²

Provocative observations have been made on the association between estrogen and COX-2. The expression and enzymatic activity of COX appears to vary in relation to hormonal status. Ovariectomized rats had significantly lower COX enzymatic activity than sham operated animals. However, administration of estradiol and progesterone in ovariectomized rats yields significant up-regulation of COX activity.⁴³ Another compelling observation is that PGE₂ stimulates the synthesis of estrogen proximal to breast tumor tissue by activating aromatase, a chief enzyme in the biosynthesis of estrogen.⁴⁴ Together, these results suggest a reciprocal promoting effect wherein estradiol increases COX-2 activity and the subsequent COX-2 by-product, PGE₂, further stimulates increased estrogen biosynthesis. Further work is needed to confirm these observations, which may ultimately explain the deregulation of estrogen biosynthesis and metabolism that accompanies breast cancer.

Equally provocative is the correlation between COX-2 and HER-2/neu status. A study presented at the March 2001 meeting of the American Association for Cancer Research reported that COX-2 was overexpressed in 80% of HER-2/neu-positive ductal, lobular, or infiltrating breast cancers evaluated.⁴⁵ Previous investigations into the nature of the relationship between COX and HER-2/neu have employed colorectal cancer models. Thwarting HER-2 signaling produces an unexpected reduction in COX-2 expression; conversely, activation of the HER-2 pathway up-regulates COX-2 mRNA and protein and produces an accumulation of PGE₂ in the culture medium.⁴⁶ Whereas either celecoxib or Herceptin[®] inhibit HCA-7 colon cancer cell growth in vitro and in vivo, combination therapy results in additive effects.⁴⁷ A trial sponsored by the National Cancer Institute (NCI) on the combined use of celecoxib and Herceptin[®] in women with metastatic breast cancer is currently under way.

Gastric Cancer

In vitro research on various gastric cancer cell lines provides supportive evidence that COX-2 is related to their cell proliferation. In this research, COX inhibition—via indomethacin or a selective COX-2 inhibitor (NS-398)—suppresses proliferation of gastric cancer cells that overexpress COX-2 (MKN45) but has mini-

mal effects on cell lines with lower COX-2 expression (KATOIII and MKN28).⁴⁸ Exposure of SNU-216 gastric cancer cells to selective COX-2 inhibitors shows potent cytotoxicity via apoptosis.⁴⁹

Examinations of COX-2 expression in patients with gastric cancer reveal a central role for COX-2 in this type of cancer. COX-2 overexpression is demonstrated in human gastric adenocarcinoma biopsy specimens but absent in adjacent histologically normal tissue.^{49,51} Whereas one study reports no correlation between COX-2 expression and the clinico-pathological characteristics of gastric adenocarcinoma patients,⁵² other studies have noted a significant relationship. For example, COX-2 mRNA expression is significantly correlated with the depth of invasion,⁵¹ lymph node involvement,⁵³ and vascular invasion.⁵⁴ In the latter study, patients with COX-2 positive gastric adenocarcinoma had significantly poorer prognosis than those with COX-2 negative tumors.⁵⁴ There was no relationship between COX-1 and prognosis or clinicopathological factors.

Gynecological Cancers

Tissue specimens from patients with adenocarcinoma or squamous cell carcinoma of the uterine cervix show up-regulation of COX-2 mRNA and protein, elevated synthesis of PGE₂, and increased expression of PGE₂ receptors.^{55,56} These findings were absent in specimens of normal cervix. Endometrial carcinoma shows a similar pattern, with COX-2 expression evident in endometrial carcinoma and hyperplasia but absent in normal endometrium.⁵⁷

COX-2 appears to correlate with the invasive potential of gynecological cancers, and COX-2 values have prognostic significance in cervical cancer. COX-2 overexpression is correlated with lymph-vascular space invasion in both endometrial⁵⁷ and cervical cancer,⁵⁸ with COX-2 staining particularly strong at the tumor invasion site. A study of 24 patients with cervical carcinoma treated with radiotherapy evaluated the prognostic value of tumor size, stage and grade, radiotherapy dose, pretreatment and posttreatment hemoglobin levels, and COX-2 distribution staining. Decreased COX-2 staining was the only factor associated with improved survival. Five-year survival rates for patients with low-versus high-tumor COX-2 values were 75% and 35% respectively.⁵⁹

Considered together, these studies suggest a role for COX-2 and PGE₂ in cervical and endometrial cancers.

Head and Neck Cancer

Evidence to date confirms a role for COX-2 and PGE₂ in tumor cell proliferation, invasiveness, and metastasis in squamous cell carcinoma of the head and neck

(HNSCC). COX-2 protein is detected in all cases of patients with HNSCC but is undetectable in normal mucosa, and a comparison of COX-2 mRNA demonstrates a nearly 100-fold increase in HNSCC compared to controls.^{60,61}

Selective inhibitors of COX-2 suppress the growth of human HNSCC in a murine xenograft model.⁶² COX-2 inhibition also impedes the *in vitro* proliferation of a squamous cell carcinoma cell line (NA), which constitutively expresses COX-2 mRNA.⁶³ This inhibitory effect is reversed with the addition of PGE₂, suggesting that COX-2 blockage inhibits the proliferation of cancer cells *in vitro* via suppression of PGE₂ synthesis.

An evaluation of COX-2 mRNA and protein, and PGE₂ levels in 35 patients with HNSCC lends support to the relationship between COX-2 and tumor progression. In this study, PGE₂ levels were higher in the tumor front zone than in tumor core or normal mucosa. Lymph node metastasis was associated with higher COX-2 protein expression and greater PGE₂ levels.⁶¹ The researchers also reported a significant correlation between COX-2 values and vascular endothelial growth factor (VEGF) expression in tumor tissue and between COX-2 and tumor vascularization.

Lung Cancer

COX-2 expression is detected in 70% to 80% of human adenocarcinoma and its precursor lesions.⁶⁴ Furthermore, there is a differential level of gene expression depending on tumor type. COX-2 levels in non-small cell lung cancer (NSCLC) are greater than COX-2 values in adenocarcinoma, which in turn exceed those found in squamous cell carcinoma.^{65,66}

Research on COX-2 null mice lends support to the role of host-derived COX-2 in tumor growth, and possibly angiogenesis, in Lewis lung carcinoma. The growth of implanted Lewis lung carcinoma *in vivo* is markedly attenuated in COX-2 null mice but unchanged in COX-1 null or wild-type mice.⁶⁷ In addition, decreased vascular density is observed in tumors grown in COX-2(-/-) mice compared to that in wild-type mice.

The COX-2 inhibitor nimesulide inhibits the proliferation—in part via inducing apoptosis—of NSCLC cell lines *in vitro* in a dose-dependent manner, even at clinically achievable low concentrations.⁶⁸ The inhibitory effect appears to be independent of p53 status. Notably, responsiveness of NSCLC lines to COX-2 inhibitors in this study did not require the presence of wild-type p53, but may be influenced by the degree of COX-2 expression.

A recent clinical study indicates that the presence of COX-2 is associated with a negative prognosis in stage I lung cancer patients.⁶⁹

Pancreatic Cancer

Preliminary investigations offer tentative support for the association of COX-2 in pancreatic cancer, specifically, but much additional work is needed to characterize the role of COX-2 and PGE2 in tumor viability, invasion, and metastasis. Levels of COX-2 mRNA are increased greater than 60-fold in pancreatic cancer compared to adjacent nontumorous tissue, and COX-2 protein is present in cases of adenocarcinoma of the pancreas but undetectable in nontumorous pancreatic tissue and weak or absent in benign tumors.⁷⁰⁻⁷³

COX inhibitors (sulindac, indomethacin, and methanesulfonamide) inhibit cell growth in both COX-2 positive and negative cell lines; however, growth suppression is significantly greater in COX-2+ cell lines.⁷³ The growth inhibitory effect of aspirin on 4 pancreatic cancer cell lines parallels their level of COX-2 expression.⁷⁴ Despite these provocative *in vitro* and *in vivo* findings, the only study to date that has examined the relationship between COX-2 expression and prognosis in pancreatic cancer patients finds no significant correlation.⁷¹

Prostate Cancer

NSAID use has a documented chemopreventive effect against prostate cancer. Regular daily use of over-the-counter or prescription NSAIDs significantly decreased the risk of prostate cancer (odds ratio: 0.35; 95% confidence interval: 0.15-0.84) in a case control study.⁷⁵ These findings represent a risk reduction of NSAIDs against prostate cancer surpassing that previously reported for colon cancer⁸ and breast cancer.³³

In vitro and *in vivo* research links both PGE2 and COX-2 to prostate tumor growth and suggests their potential role in prostate cancer progression. The COX-2 substrates, linoleic acid and arachidonic acid (AA), as well as the COX-2 by-product PGE2, stimulate cell proliferation and tumor growth *in vitro* in PC-3 human prostate cancer cells.^{76,77} In PC-3, LNCaP, and DU145 prostate cancer cell lines, up-regulation of COX-2 and PGE2 is inversely correlated with apoptosis.⁷⁸ COX-2 inhibitors suppress PC-3 tumor growth *in vivo*, achieving this effect via the induction of tumor cell apoptosis, down-regulation of VEGF, and decreased angiogenesis.⁷⁹

COX-2 mRNA and protein levels are present in normal prostate epithelial cells, suggesting COX-2 may play an important role in healthy prostate function. Nonetheless, COX-2 mRNA levels are 3.4-fold higher in prostate cancer tissue compared to pair-matched benign tissue from the same patient.⁸⁰ Patients with high levels of peritumoral inflammation in radical prostatectomy specimens had significantly more post-operative biochemical recurrence than patients with

low levels of inflammation.⁸¹ An NCI-sponsored, phase I trial of neoadjuvant celecoxib following prostatectomy in patients with localized prostate cancer is due to open shortly at Johns Hopkins Oncology Center in Baltimore, Maryland.

Urinary Bladder Cancer

Findings similar to those presented thus far in other cancers exist for the association of COX-2 in urinary bladder cancer. COX-2 overexpression is documented in urinary bladder tumors and metastatic lesions but is undetected in normal bladder epithelium.^{82,83} Whereas noninvasive tumors display homogeneous patterns of COX-2 staining, tissue examinations of human transitional cell carcinoma of the bladder demonstrate COX-2 staining intensity is strongest among the invading cells of invasive carcinomas.⁸⁴ This observation suggests COX-2 is involved in the invasive process.

Administration of a selective COX-2 inhibitor can achieve chemoprevention of rat urinary bladder cancer.⁸⁵ Further animal studies show the addition of various COX-2 inhibitors to carcinogen-induced bladder tumors results in a dose-dependent reduction in tumor burden.^{86,87}

COX-2 expression appears significantly correlated with tumor stage: 93% of human carcinoma *in situ* specimens expressed COX-2 whereas only 48% of dysplasia samples expressed COX-2.⁸³ This differential expression profile suggests COX-2 may be involved in the development of transitional cell carcinoma of the urinary bladder.

An NCI-sponsored, phase II/III clinical trial on celecoxib for prevention of recurrent bladder cancer is under way at the University of Texas, M. D. Anderson Cancer Center.

What Causes COX to Be Elevated/Up-Regulated in Cancer?

Further research is needed on the mechanisms responsible for COX-2 up-regulation in neoplasia. Preliminary investigations suggest COX-2 is inducible by certain oncogenes (e.g., ras and scr), interleukin-1 (IL-1), hypoxia, benzo[a]pyrene, ultraviolet light, epidermal growth factor, transforming growth factor beta (TGF- β), and tumor necrosis factor alpha (TNF- α).⁸⁸ Together with the promoting action of various signaling molecules in cancer pathophysiology, there appears to be a positive feedback loop wherein increased action of COX-2 produces greater concentrations of PGE2, which in turn further increases the expression of COX-2. Treatment with epidermal growth factor (EGF) induces COX-2 protein and COX-2 mRNA and stimulates COX-2 promoter activity in cervical cancer cell lines.⁸⁶ Of note, PGE2 has been shown to up-regu-

late gene expression of its synthesizing enzyme, COX-2, in prostate, breast, and colon cancer cell lines.^{77,89}

Physiopathological Events Associated with COX-2

Thus far, an examination of the impact of COX-2 overexpression in various types of cancer has been presented. But how does COX-2 exert its influence on the malignant phenotype? To date, several mechanisms have been identified by which COX-2, and its by-product PGE2, may contribute to tumor viability and progression:⁹⁰

1. Promotion of cell proliferation
2. Inhibition of apoptosis
3. Increased angiogenesis
4. Increased invasiveness (and metastases)
5. Immunosuppression.

A review of the relevant literature on these mechanisms follows.

Cell Cycle and Proliferation

Both COX-2 and PGE2 appear to have direct effects on cell proliferation. Tumor cells that lack the ability to express COX-2 proliferate very slowly *in vivo*.⁹¹ Exogenous PGE2 increases cellular proliferation in various cell lines, including LNCaP (androgen-dependent) and PC-3 prostate cancer cells, breast cancer MDA-MB-134 cells, and human colorectal carcinoma DiFi cells.^{77,92,93} Cell cycle arrest, or shift in profile of cell cycle parameters, has been documented *in vitro* with NSAIDs.^{94,95} Some criticism is due portions of the NSAID research for the large doses used to achieve growth inhibitory effects, which are not achievable clinically and are supraphysiologic to the small doses required for COX inhibition. However, Eli et al.⁹⁴ showed low-dose NSAIDs were effective in growth inhibition and cell cycle arrest *in vitro*, and attenuation of the growth of primary tumors and their metastases *in vivo*.

Apoptosis

COX-2 expression and apoptosis appear to be inversely correlated. COX-2 inhibitors have been documented to induce apoptosis *in vitro* in NSCLC,⁶⁸ gastric cancer,⁴⁹ and human colon cancer cell lines.⁷ It is unknown whether the decrease in programmed cell death can be attributed to a diminished AA content of cell membranes, increased PGE2 (or other prostanoid) levels, or via the direct action of COX-2. Decreased cellular levels of unesterified AA appear to regulate apoptosis.⁹⁶ Another study notes COX-2 mediated suppression of apoptosis may be controlled by increased PGE2 levels (which modulate pro-apoptotic and anti-

apoptotic factors such as bcl-2, MAKS/ras, caspase-2, and Par-4).⁹⁰ Further research is needed to characterize the nature of the relationship between inflammatory events and apoptosis.

Angiogenesis

Studies to date suggest a functional role for COX-2 and inflammatory eicosanoids in tumor-induced angiogenesis. This is not surprising given the known effect of inflammation in normal angiogenesis, but appears to be excessive and long lasting in tumor angiogenesis.

Under normal physiological conditions, quiescent vasculature expresses only constitutive COX-1 whereas COX-2 expression is observed in newly formed blood vessels within and surrounding tumors in both animals and humans.^{70,97,98} Vascular density is approximately 30% lower in tumors grafted into COX-2 null mice compared with tumors grown in animals with the active COX-2 gene.⁶⁷ COX-2 overexpression in human tumor specimens is directly correlated with microvessel density in metastasized HNSCC,⁶¹ NSCLC,⁹⁹ gastric cancer,⁵³ and colorectal carcinoma.²⁶

Treatment with selective inhibitors of COX-2 effectively suppresses angiogenesis in *in vivo* models of many types of cancer.¹⁰⁰⁻¹⁰³ Several mechanisms appear to contribute to the pro-angiogenic effects of COX-2. Increased production of eicosanoid by-products (e.g., PGE2, TXA2, and PGI2) may potentially reduce endothelial cell apoptosis and directly stimulate endothelial cell migration.^{104,105} COX-2 and its prostaglandin by-products increase the expression of pro-angiogenic growth factors, such as basic fibroblast growth factor, platelet-derived growth factor, and VEGF.⁹⁰ In numerous studies, the anti-angiogenic effect of COX-2 inhibitors appears to be mediated through down-regulation of VEGF.^{79,97,106-109} Fibroblasts from COX-2 null mice have a 94% reduction in the ability to produce VEGF, and the treatment of wild-type mouse fibroblasts with a selective COX-2 inhibitor reduced VEGF production by 92%.⁶⁷ Tumors grown in COX-2 null mice have significant reductions in VEGF expression.¹¹⁰

Invasion and Metastasis

COX-2 (and other inflammatory mediators) have a role in tumor invasiveness and metastasis. NSAIDs and selective COX-2 inhibiting agents reduce invasiveness of human prostate cancer cell lines, PC-3 and DU-145, *in vitro*, and the effect can be reversed by the addition of PGE2.¹¹¹

Both *in vitro* and *in vivo* research suggest that COX-2 inhibition may be a potent approach to inhibit the metastasis of colorectal cancers. Of 4 colon cancer cell lines investigated, the most invasive and metastatic

variant (HT-29/Inv3) expresses the highest COX-2 values and PGE2 production: etodolac, a COX-2 inhibitor, markedly suppresses the invasive property of this cell line in vitro.¹¹² COX-2 inhibitor treatment of mice with a highly metastatic colon cancer (LM-H3) reduced the mean number of hepatic metastases in vivo from 46.4 ± 18.9 nodules in controls to 3.6 ± 2.9 nodules in treated mice.¹¹³ Selective COX-2 inhibition has also been shown to significantly reduce the number of lung metastases from colon cancer in mice.¹¹⁴

In human colorectal cancer patients, high COX-2 expression significantly correlates with tumor recurrence and hematogenous metastases.²⁸ Excessive production of PGE2 has been linked with both tumor metastasis to bone and poor survival in breast cancer patients.¹¹⁵ In patients with endometrial carcinoma, those with lymph-vascular space invasion demonstrate increased COX-2 staining compared to those without evidence of invasion.⁵⁷ In gastric carcinoma specimens, COX-2 overexpression in tumors is significantly correlated with local tumor invasion and lymph node metastasis.¹¹⁶

COX-2 may increase the invasive properties of tumors by up-regulating metalloproteinases (e.g., MMP-2), thereby resulting in increased tumor cell migration.^{90,111} COX inhibitors significantly reduce levels of MMPs in culture.^{111,113}

Immune Suppression

A detailed investigation of the complex interactions between inflammatory events and host immune response is beyond the scope of this article. A brief survey shows contradictory findings, which perhaps can be explained by this statement: at low levels, inflammation enhances immune response, but when excessive or prolonged, it suppresses immune function.¹¹⁷ This correlation may be explained by the difference between COX-1 and COX-2 mediated inflammatory events. Tumor-derived PGE2 appears to modify cytokine balance and impair host immunocompetence.¹¹⁸ Tumor-derived PGE2 plays a pivotal role in promoting the production of IL-10 (a potent immunosuppressive cytokine) by lymphocytes and macrophages while simultaneously inhibiting IL-12 production.^{119,120} In addition, PGE2 can inhibit the functional activity of lymphokine-activated killer cells and natural killer cells.¹²¹⁻¹²³ These findings suggest that abrogation of excessive inflammatory response may promote antitumor reactivity by restoring the balance of IL-10 and IL-12 in vivo and enhancing the function of natural killer cells.

Complementing Conventional Therapies

A promising area of therapeutic application for anti-inflammatory agents is as adjuncts to conventional

treatments, such as surgery, radiotherapy, and chemotherapy.

Surgery

Because surgery provokes an inflammatory response, and because inflammatory events may promote tumor growth and angiogenesis, the therapeutic efficacy of cancer surgery may hypothetically be increased with concomitant administration of anti-inflammatory agents. Some research supports this hypothesis. Specifically, radical nephrectomy for renal cell carcinoma is controversial. When preoperative markers of inflammation are low, median survival of patients is significantly better in those who do not elect surgery (80.6 months) compared to those who do (50.2 months). In patients with elevated inflammatory markers, however, there is no difference in treatment outcome between the 2 groups.¹²⁴ A similar relationship has been demonstrated in hepatocellular carcinoma, wherein up-regulated COX-2 expression in nontumorous samples of hepatic tissue was associated with increased rates of relapse and shorter disease-free survival.¹²⁵ The implication of these findings is that when inflammation status is normal, tumor progression is slow and surgical treatment may actually worsen the prognosis. Conversely, surgical resection may increase its therapeutic efficacy when combined with steps to effectively control inflammation. In patients with elevated inflammatory markers preoperatively, it may be prudent to first pursue an aggressive anti-inflammatory protocol before proceeding with surgery. Investigations to test these hypotheses are an urgent priority.

Radiotherapy

COX-2 inhibition may act as a radiosensitizer. Recently published studies employing animal models have demonstrated that selective COX-2 inhibitors can augment tumor response to radiotherapy without increasing the radioresponse of normal tissues.^{32,126,127} For example, administration of a selective COX-2 inhibitor enhanced radiation-induced cell death in an additive manner in COX-2 expressing human glioma cell line (U251) both in vitro and in vivo.³² The mechanism of action responsible for these effects is unknown and deserves further investigation. One possible explanation may be the antiangiogenic effects of COX-2 inhibitors, described above. Cotreatment with an angiogenesis inhibitor (e.g., TNP-470) greatly improves tumor radioresponse in mice with human glioblastoma xenografts.¹²⁸ Glioblastoma multiforme is a particularly aggressive and frequently radio-resistant human brain tumor. Taken together, these studies suggest a large potential for improving radioresponse of tumors with COX-2 inhibitors, which have direct radiosensitizing

properties and may also enhance radioresponse via angiogenesis inhibition.

Chemotherapy

Anti-inflammatory drugs may also have the potential to increase the cytotoxic effects of chemotherapy. In T98G human malignant glioma cell lines, NSAIDs enhance the cytotoxic effects of doxorubicin and vincristine, but not carmustine (1,3-bis [2-chloroethyl]-1-nitrosourea), cisplatin, and several other agents.¹²⁹ This potentiation was achieved independent of free-radical formation or free-radical scavenging effects. The COX-2 inhibitor, nimesulide, potentiates the effects of doxorubicin in human colon carcinoma and lung cancer cell lines by 36% and 61%, respectively.¹³⁰ At clinically achievable concentrations, nimesulide reduced IC₅₀ values of various anticancer agents by up to 77% in NSCLC cell lines.⁶⁶

Although further research is needed to elucidate the mechanisms of action of this potentiation, the recent finding that COX-2 inhibition may offer anti-angiogenesis effects, as well as separate findings that angiogenesis inhibition appears to provide additive therapeutic benefit to chemotherapy, suggests a potential mechanism for this finding.¹⁰⁴ Of note, NSAIDs should not be given concurrently with methotrexate, due to their ability to greatly boost blood levels of the drug, leading to serious complications (e.g., diarrhea, fever, ulceration of mouth and gastrointestinal tract, nausea, vomiting, kidney failure, blood abnormalities due to bone marrow damage, and death).¹³¹

Cancer-Related Pain

Anti-inflammatory agents also have a role in the management and control of cancer pain, perhaps delaying the need for narcotic agents. Tissue damage from tumor or treatment is associated with increased prostaglandin production, which can subsequently sensitize pain receptors, reducing their response threshold for prostaglandin stimulation.¹³²

Broadening the Scope of Vision: Beyond COX-2

An expansive body of research has focused in the past 5 years on the relationship between COX-2, its by-product PGE₂, and cancer. This focus continues today, and is perhaps driven by the pharmaceutical market for agents that selectively inhibit COX-2 (celecoxib and rofecoxib). In summary, the pathological overexpression of COX-2 appears to be related to key events in tumor promotion, such as cellular hyperproliferation, inhibition of programmed cell death, and tumor angiogenesis. COX-2 expression is up-regulated dur-

ing tumorigenesis and by tumor promoters, and tumor number and growth are affected by modulation of COX-2 (as in COX-2 null mice). COX-2 inhibitors—and in some cases NSAIDs—reduce tumor growth in vitro and in vivo. COX-2 overexpression is documented in the malignant tissues of cancer patients and typically correlates with tumor size, tumor stage, tumor metastasis, and patient survival. These effects have been documented in a wide variety of epithelial-type tumors: cancers of the breast, colon, head and neck, brain, lung, pancreas, urinary bladder, and others. Taken as a whole, the research on COX-2 implies the conclusion that efficient tumor growth requires the presence and action of COX-2 in the tumor host and that abrogation of COX-2 imparts chemopreventive effects and potential benefits in cancer treatment. However, is this a complete picture of inflammatory events and cancer?

Despite the preponderance of research on COX-2 and its resulting series-2 prostaglandins, there are numerous additional eicosanoids and alternate enzymatic pathways for their metabolism. Eicosanoid by-products of AA, for example, may be produced not only by COX but also via lipoxygenase (LOX) and cytochrome P450. These eicosanoids are generated by most cancers and appear to play a significant role in promoting the induction, proliferation, angiogenesis, and spread of cancers.¹³³ An overview of eicosanoid metabolism is presented next, followed by a brief review of the research on leukotrienes and its implication in cancer.

Eicosanoid Biosynthesis

Eicosanoids are biosynthesized from the fatty acid components of the phospholipid structure of cell membranes, the composition of which is directly dependent on sources of fatty acids in the diet. Eicosanoids fall into 3 general groups, prostaglandins, leukotrienes (LTs), and thromboxanes, all arising from 20-carbon (hence their prefix, “eicosa”) fatty acids: AA (20:4w6), eicosapentaenoic acid (EPA, 20:5w3), or dihomo-gammalinolenic acid (DGLA, 20:3w6). The eicosanoids produced by these fatty acids have differing actions, ranging from the highly pro-inflammatory action of AA-derived compounds to the weakly inflammatory, and thereby favorable, actions of EPA-derived compounds.

Fatty acids are released from membrane phospholipids via the action of phospholipase A₂ and then acted upon by COX and LOX. Figure 1 shows the biosynthesis of various eicosanoids.

AA is derived from dietary sources, such as meat, dairy products, and eggs, and can also be biosynthesized from omega-6 fatty acids of vegetable

origin. There are 3 known enzymatic pathways for the synthesis of eicosanoids from AA. In the first, COX generates short-lived endoperoxides (e.g., PGG and PGH) that are immediately converted into series-2 prostaglandins (e.g., PGE₂, PGF₂- α) and thromboxanes (e.g., TXA₂, TXB₂). The second pathway involves the LOX group of enzymes, which create hydroperoxy-eicosatetraenoic acids (HpETEs). HpETEs are converted into series-4 LTs and various hydroxy-eicosatetraenoic acids (e.g., 5-HETE, 12-HETE, 15-HETE). The third pathway involves cytochrome P-450, which can directly catalyze the formation of 12-HETE and 16-HETE. AA-derived compounds have potent pro-inflammatory effects, increase pain, increase vasoconstriction, and promote thrombosis.

DGLA is near nonexistent in the diet and is mostly derived from vegetable-source omega-6 fatty acids (nuts, seeds, and vegetable oils). DGLA is metabolized by the action of COX to create series-1 prostaglandins (e.g., PGE₁) and thromboxanes (e.g., TXA₁). LOX metabolizes DGLA to create series-3 LTs. Series-1 prostanoids function to dilate blood vessels, prevent platelet aggregation, lower arterial pressure, inhibit thrombosis, inhibit cholesterol synthesis, and inhibit inflammation.¹³⁴

The action of COX upon EPA creates series-3 prostaglandins (e.g., PGE₃) and thromboxanes (e.g., TXA₃). LOX metabolizes EPA to create series-5 LTs (e.g., LTB₅). Dietary sources of preformed EPA are cold-water fish. EPA can also be created via enzyme biosynthesis of omega-3 fats, such as linolenic acid (18:3w3) from linseed (flax) oil, and certain other oils. EPA-derived eicosanoids block the production of series-2 compounds and offer anti-inflammatory effects.¹³⁴

Dietary intake of fatty acids is a primary determinant of eicosanoid metabolism. The total concentration of fatty acids present in the phospholipid structure of the cell membrane determines which class of eicosanoid by-products will predominate. Therefore, there is a direct link between the balance of specific fats in the diet and inflammatory responses.¹³⁵ Reduction of dietary AA intake is paramount. However, this observation often leads to an inappropriate recommendation: reduction of AA intake, but an additional emphasis on both omega-6 and omega-3 fatty acids, which are precursors of PGE₁ and PGE₃, respectively. It is important to note that the omega-6 fatty acid DGLA can be diverted by delta-5 desaturase (Δ 5D) to produce AA and the inflammatory series-2 prostanoids (see Figure 1).

Another important consideration governing therapeutic intake of dietary fats is substrate competition, as pictured in Figure 1. AA and omega-6 and omega-3

polyunsaturated fats must compete for active binding sites on desaturase, elongase, COX, and LOX. Thus, the predominant dietary fat present in a cell phospholipid will determine the direction of eicosanoid production.¹³⁵

The binding affinity of desaturase enzymes increases with the number of double bonds present in the substrate fatty acid.¹³⁵ For example, EPA (20:5W3) will bind delta-5 desaturase stronger than DGLA (20:3w6). However, in the absence of adequate EPA, omega-6 metabolism is unchecked, favoring the production of AA and generation of pro-inflammatory compounds.

The activity of desaturase is suppressed by excessive intake of dietary saturated, monounsaturated, and trans fats, insulin excess, and magnesium and/or zinc deficiency.^{134,135}

A nonenzyme-mediated pathway for the production of inflammatory compounds has also been discovered. Free-radical catalyzed peroxidation of AA produces isoprostanes, a stable isoform of prostaglandins that have much stronger inflammatory effects.¹³⁴

Adequate control of inflammatory pathways must take these considerations into the balance. Merely blocking COX does not address the accumulation of substrate AA, which can alternately be metabolized by LOX. LOX by-products, the LTs and HETEs, are also implicated in tumor growth and progression, and these effects are reviewed next.

Effects of LOX, LTs, and HETEs in Cancer

LOX by-products (5-HETE and 12-HETE) have prominent roles in the progression of cancer.¹³⁶ Limited evidence to date suggests that, depending on the type of cancer, LTs may play an even greater role than prostaglandins in stimulating tumor growth.^{92,137-144} Unlike prostaglandins and thromboxanes, which are short lived and synthesized only according to immediate need and then rapidly degraded, LTs are quite stable, with a half life approaching 4 hours.¹⁴⁵ The impact of LTs on various types of cancer is summarized in Table 2.

COX-dependent moieties have been noted to decrease, and LOX by-products, LTB₄ and 12-HETE, to increase considerably following tumor implantation in animals.¹⁴⁶ Gliomas produce 5-HETE and use it as an autocrine growth factor stimulating their proliferation and suppressing apoptosis; consequently, LOX inhibitors have demonstrated significant inhibitory effect on in vitro growth rate and cell proliferation in human glioma cell lines.¹⁴⁷⁻¹⁴⁹ LOX inhibitors also exert growth inhibitory effects and apoptosis-inducing effects in vitro against human leukemia cell lines,¹⁵⁰⁻¹⁵³ MDA-MB-231 human breast cancer cells,^{154,155} and human colon cancer cell lines (HT-29 and HCT-15).⁹² In some instances, LOX inhibitors demonstrated

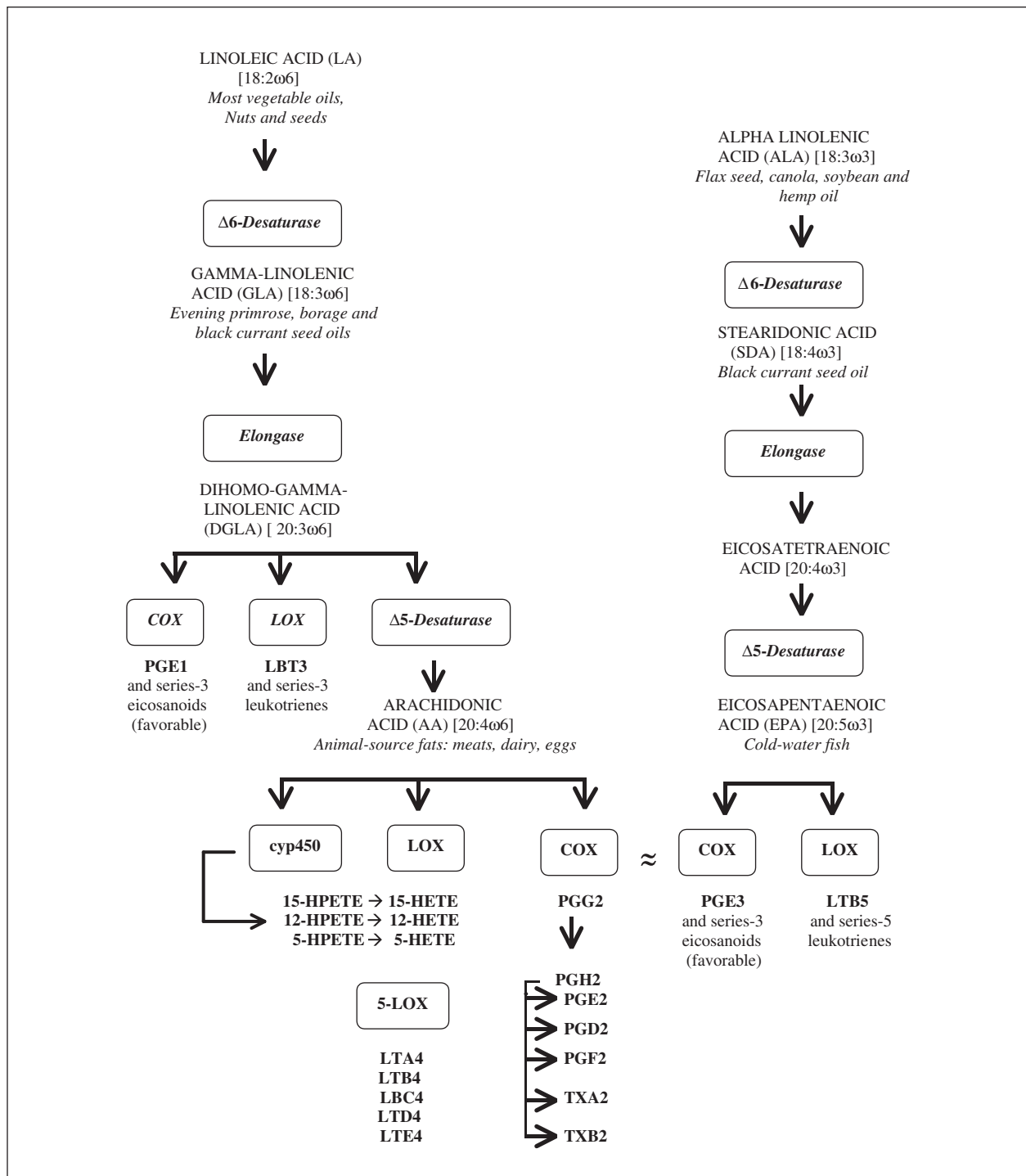


Figure 1 Biosynthesis of eicosanoids

growth inhibitory effects whereas COX inhibitors had no effect.^{149,153}

While the growth of MCF-7 breast cancer cells appears to be associated with both prostaglandin and LT production, incubation with a LOX-inhibiting agent (nordihydroguaiaretic acid) was more inhibitory of cell growth in vitro in the presence of linoleic acid than a COX inhibitor (indomethacin).¹⁵⁶ Tumor growth

of murine adenocarcinomas may be inhibited in vivo by LOX inhibitors.¹⁵⁷

When the levels of COX and LOX metabolites of AA were measured in the saliva of patients with HNSCC and compared with controls who had no history of cancer, LTB4 was significantly increased in cancer patients, but no significant differences were observed in PGE2 levels.¹⁵⁸

Table 2. Research on Lipoxygenase (LOX) By-Products (LTB4, 5-HETE, and 12-HETE) in Various Cancers

Brain cancer		
Blomgren and Kling-Andersson (1992)		LOX inhibitors block DNA synthesis in glioma cell lines more potently than COX inhibitors ¹⁴⁹
Gati et al. (1990)		Potent, dose-dependent inhibition of proliferation of human glioma cell lines by agents that block LOX ¹⁴⁷
Gati et al. (1990)		5-LOX inhibitors induce apoptosis in human glioma cell lines ¹⁴⁸
Breast cancer		
Cunningham et al. (1997)		Incubation of MCF-7 cells with a LOX inhibitor was more inhibitory of cell growth in vitro than a COX inhibitor (indomethacin) ¹⁵⁶
Liu et al. (1996)		12-LOX transfected human breast cancer cells have enhanced growth in vitro ⁴¹
Natarajan and Nadler (1998)		12-HETE promotes proliferation of breast cancer cells in vitro ¹⁶³
Connelly and Rose (1998)		Enhanced growth in 12-LOX transfected human breast cancer cells in vitro ¹⁷¹
Earashi et al. (1996)		LOX inhibitors suppress growth of MDA-MB-231 cells in vitro ¹⁵⁴
Tripathi et al. (1996)		MDA-MB-231 cell growth in vitro suppressed by LOX or COX inhibition ¹⁵⁵
Leukemia		
Anderson et al. (1994, 1996)		Inhibitors of 5-LOX induce apoptosis in vitro ^{150,152}
Anderson et al. (1995)		Selective inhibitors of 5-LOX reduce blast cell proliferation and induce differentiation in chronic myelogenous leukemia ¹⁵¹
Snyder et al. (1989)		LOX inhibitors have growth inhibitory effects against human leukemia cell lines ¹⁵³
Colon cancer		
Bortuzzo et al. (1996)		LTB4, 12-HETE stimulate proliferation in 2 human colon cancer cell lines (HT-29 and HCT-15) in vitro; the effect is reversed with an LTB4 antagonist ⁹²
Head and neck cancer		
Scioscia et al. (1997)		Treatment with a LOX inhibitor (ketoconazole) resulted in significant inhibition of tumor growth and reduced tumor weight in a murine model of squamous cell carcinoma of the head and neck ³⁶³
Ondrey et al. (1996)		Leukotriene inhibition (but not prostaglandin inhibition) markedly decreases DNA synthesis and cell proliferation in squamous carcinoma cell line SCC-25 ¹³⁷
Malone and Snyderman (1994)		Levels of LTB4, but not PGE2, significantly elevated in squamous cell carcinoma of the head and neck patients compared to patients with no history of cancer ¹⁵⁸
Melanoma		
Winer et al. (2001)		12-HETE plays a crucial role in promoting experimental melanoma invasion and metastasis; may be a marker for cancer progression in melanoma patients ¹⁷³
Prostate cancer		
Myers and Ghosh (1999)		PC3 and LNCaP cells convert arachidonic acid to 5-HETE; when formation of 5-HETE is blocked in vitro, human prostate cancer cells enter apoptosis in less than 1 hour and are dead within 2 hours; exogenous 5-HETE can rescue these cells, suggesting 5-HETE is a potent survival factor for human prostate cancer cells in vitro ¹⁶¹
Ghosh and Myers (1998)		Inhibition of 5-LOX, which completely blocks 5-HETE production, induces massive and rapid apoptosis in LNCaP and PC-3 cells in vitro ¹⁶⁰
Anderson et al. (1998)		A 5-LOX inhibitor reduces proliferation in PC-3 cells in vitro ³⁶⁴
Liu et al. (1997)		12-HETE increased motility of prostate cancer cells via selective activation of protein kinase C alpha ¹⁷²
Ghosh and Myers (1997)		5-HETE stimulates proliferation of prostate cancer cells in vitro; selective inhibition of COX, 12-LOX, 5-LOX, and CP-450 shows 5-LOX to be most growth stimulatory; prostate cancer cells fed arachidonic acid have dramatic increase in 5-HETE production ¹⁵⁹ ; prostate cancer cells fed
Gao et al. (1995)		Elevated 12-LOX mRNA correlates with advanced stage and poor differentiation in human prostate cancer ¹⁶⁴
Pancreatic Cancer		
Ding et al. (1999)		12-HETE promotes proliferation of pancreatic cancer cells, and LOX inhibitors abolish the proliferation of human pancreatic cancer cells in vitro ¹⁶²

The role of 5-HETE has been particularly well investigated in prostate cancer cell lines. Exogenous AA markedly increases 5-HETE production by prostate cancer cell lines. When formation of 5-HETE is blocked, both hormone-responsive (LNCaP) and nonresponsive (PC-3) human prostate cancer cells quickly undergo programmed cell death in vitro.¹⁵⁹⁻¹⁶¹ Addition of exogenous 5-HETE can rescue these cells, suggesting 5-HETE is a potent survival factor for human prostate cancer cells.

12-HETE promotes the proliferation of human colon carcinoma cell lines,⁹² pancreatic cell lines,¹⁶² and breast cancer cell lines.¹⁶³ Elevated 12-LOX mRNA correlates with advanced stage and poor differentiation in human prostate cancer.¹⁶⁴ 12-HETE plays an important role in cell adhesion and promotion of metastasis.¹⁶⁵⁻¹⁷¹ These effects of 12-HETE appear to be mediated via the activation of protein kinase C.¹⁷² 12-HETE appears to play a crucial role in experimental melanoma invasion and metastasis, and has been suggested

as a novel marker for cancer progression of melanoma.¹⁷³

LTs may also be involved in regulating angiogenesis. They have been reported to stimulate angiogenesis in some tissues without assistance from growth factors.^{174,175} For example, 12-LOX appears to stimulate angiogenesis in human prostate carcinoma cells¹⁷⁰ and human breast cancer¹⁷¹ in vivo. LTs may induce angiogenesis in part via inducing NF-kappaB (NFKB). Inhibition of LT activity may reduce NFKB-induced angiogenesis. Conversely, NFKB activity may induce angiogenesis in part by promoting LT production (NFKB appears to act as a transcription factor for the genes that control LOX and COX production).¹⁷⁶

Because a majority of studies that have examined the role of prostaglandins have failed to control for the effects of LTs, further carefully designed and controlled research is needed to elucidate the true impact of LOX-derived compounds.

Rationale for Natural Anti-Inflammatory Strategies

Despite epidemiologic analyses suggesting chemopreventive effects of chronic NSAID administration, the risk of toxicity limits the use of these agents in this therapeutic application. Gastric ulceration, perforation, or obstruction is reported in one third to nearly one half of chronic NSAID users.¹⁷⁷ Reports estimate 10,000 to 20,000 NSAID-related deaths and 100,000 related hospitalizations in the United States annually.¹⁷⁸ Selective COX-2 inhibitors (celecoxib, rofecoxib) have been heralded as much safer drugs. Unlike NSAIDs, they appear to have little or no increased risk of gastrointestinal bleeding or peptic ulceration. Yet, their long-term safety has yet to be documented. COX-2 is constitutively expressed in kidney, brain, spinal cord, pancreatic islet cells, osteoblasts, and reproductive tissues.¹⁷⁹ The potential risks of selective COX-2 inhibitors appear to be related to kidney, liver, or gastrointestinal complications. Of note, COX-2 is induced in the healing of wounds (such as gastric ulcer), so gastrointestinal side effects may prove problematic in patients with previously asymptomatic gastric lesions, for example, chronic NSAID users switching to Celebrex® or Vioxx®. Although concerns with regard to potential, as yet undisclosed, side effects of selective COX-2 inhibitors may limit their long-term use in chemoprevention, these concerns are unlikely to deter their successful application in the treatment of human cancers.

Perhaps a more compelling limitation of pharmaceutical COX-2 inhibitors is their inability to address LOX. Moreover, COX inhibitors may actually increase the production of LOX products via their sparing

action on AA.^{133,180,181} The administration of COX inhibitors alone as an anti-inflammatory strategy is like trying to fight a fire with a single blast of water while continuing to feed the flames with dry wood and flammable liquids.

These concerns underline the need for a nontoxic and comprehensive approach to controlling inflammatory eicosanoids. The application of natural, nontoxic anti-inflammatory strategies, which modulate both COX and LOX pathways, may be preferable in both chemoprevention and cancer therapy. The remainder of this article outlines such an approach. To date, no clinical investigations have directly tested the influence of natural anti-inflammatory approaches in cancer patients, and a call for research in that direction is appropriate.

Comprehensive Anti-Inflammatory Protocol

A comprehensive approach to modulate the impact of inflammatory eicosanoids is multifaceted. Several factors must be addressed, as summarized in Table 3.

In general, the goal of dietary modification is to reduce available substrate (AA) for the production of series-2 prostaglandins and series-4 LTs while substantially increasing the substrate for anti-inflammatory compounds, such as PGE₃. Compared to non-neoplastic cells, cancer cell membranes have greatly increased AA content, with up to 40% fatty acid composition of the cell wall as AA.¹⁸² Consumption of animal fats and omega-6 vegetable oils increases the AA content of cell membranes, particularly membranes of cancer cells.¹⁸³ Dietary sources of AA should be actively restricted, emphasizing a low-fat, plant-based diet (i.e., near-vegetarian). In addition, plant oils rich in omega-6 fatty acids—corn, safflower, peanut, soybean, sesame, and other vegetable oils—should be eliminated. Canola oil, soybean oil, black currant oil, and borage oil do contain small amounts of omega-3 fatty acids; however, these oils are abundant in omega-6 polyunsaturated fatty acids (PUFAs) and should therefore be avoided. Despite their potential to form the favorable PGE₁, omega-6 PUFAs should be limited to reduce the risk of inadvertent production of inflammatory eicosanoids via delta-5 desaturase action on DGLA, particularly in situations of elevated AA and/or deficient EPA. Over the long term, gamma linolenic acid supplementation increases tissue AA levels while decreasing tissue levels of EPA.¹⁸⁴ As previously noted, the binding affinity of desaturase enzymes increases with the number of double bonds present in the substrate fatty acid (20:3w6 < 20:4w6 < 20:5w3).

Sources of omega-3 fatty acids should be markedly increased, particularly cold-water fish, but also good

Table 3. Checklist for a Comprehensive Anti-Inflammatory Protocol

1. Restrict intake of animal-based foods: meat, dairy, poultry (dietary sources of arachidonic acid, precursor to PGE2, LTB4, 5-HETE, and 12-HETE).
2. Substantially increase dietary sources of omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid and docosahexaenoic acid: cold-water fish and fish oil supplements (precursors to series-3 eicosanoids, block metabolism of arachidonic acid).
3. Limit intake of plant-source omega-6 PUFAs, targeting a 1:1 ratio of w3 to w6 PUFAs (prevent enzyme competition and reduce inadvertent shunt to arachidonic acid and inflammatory eicosanoids).
4. Increase dietary antioxidants: 7 to 9 servings a day of deeply pigmented fruits and vegetables (reduce oxidative biosynthesis of inflammatory eicosanoids and isoprostanes).
5. Eliminate hydrogenated or partially hydrogenated and trans-fatty acids, alcohol, simple sugars, and refined carbohydrates, and reduce elevated cholesterol levels (inhibitors of desaturase).
6. Ensure adequate intake of zinc, magnesium, ascorbate, niacin, and pyridoxine (coenzymes for desaturase metabolism of omega-3 PUFAS).
7. Optimize blood glucose regulation: address hyperinsulinemia (excess insulin shifts dihomogammalinolenic acid toward PGE2 synthesis).
8. Provide a combination of several anti-inflammatory botanical agents (modulate inflammatory cascade through multiple and synergistic actions, including COX and LOX inhibition).
9. Monitor inflammatory markers (e.g., C-reactive protein, ceruloplasmin) at baseline and interval and adjust protocol as required.
10. Consider pharmaceutical COX-2 inhibitors or nonsteroidal anti-inflammatory drugs on prn basis.

quality flax seed oil. Western diets are overly abundant in sources of omega-6 fats and deficient in sources of omega-3 fatty acids, often exceeding a ratio of 10:1 to 20:1 omega-6 to omega-3 fatty acids.¹⁸⁵ Whereas in conditions of health a 4:1 ratio is considered ideal,¹⁸⁶ the therapeutic ratio in inflammatory conditions targets a 1:1 ratio. Greatly increasing the omega-3 component of the diet helps prevent enzyme competition by omega-6 fats. Desaturase enzymes favor PUFAs with higher numbers of double bonds (as indicated by the second number in their abbreviation); however, in the absence of adequate EPA (20:5w3, 5 double bonds), 6ΔD, and Δ5D will metabolize omega-6 PUFAs, AA (20:4w6), and DGLA (20:3w6), forming pro-inflammatory compounds.

Dietary fats also appear to modulate cytokine biology. A review article on the subject notes that (1) fats rich in w-6 increase the production and tissue responsiveness to cytokines, (2) w-3 rich fats decrease production and tissue responsiveness to cytokines, and (3) TNF-induced production of IL-1 and IL-6 correlates positively with linoleic acid intake.¹⁸⁷

Provision of nutrient cofactors is essential to ensure proper function of the enzymes required in the metabolism of omega-3 PUFAs. Optimal function of delta-6 desaturase requires pyridoxine, magnesium, and zinc. Delta-5 desaturase requires niacin, zinc, and vitamin C.^{134,188} A high-quality multiple vitamin and mineral product can be used to accomplish this goal. Inhibitors of desaturase—excess saturated, hydrogenated, and trans fatty acids, alcohol, hyperinsulinemia, and elevated cholesterol levels—must be reduced. Balanced blood sugar regulation, with resolution of hyperinsulinemia, can be very important in controlling inflammation because excess insulin increases Δ5D metabolism of DGLA¹⁸⁹ (refer to Figure 1), shifting

eicosanoid production away from the desirable PGE1 and PGE3 in favor of inflammatory AA metabolites.

Balanced redox status is paramount to controlling the inflammatory cascade. The diet should emphasize ample intake of pigment-rich vegetables (5 to 7 servings daily) and fruits (1 to 2 servings daily) to reduce free-radical catalyzed synthesis of isoprostanes, stable compounds with pro-inflammatory activities exceeding that of prostaglandins and LTs. Redox status can be evaluated via lab assessment, and supplemental antioxidants can be taken as needed.

Finally, nutritional and botanical anti-inflammatory agents may be employed to further modulate the inflammatory process. The application of multiple natural agents is recommended to take advantage of the synergistic effects offered by combinations of natural agents, which vary in their constituents and generally offer multiple impacts at varying points in the inflammatory cascade. Additionally, botanical selections can be made to offer both COX and LOX inhibition. Detailed information on selected nutritional and botanical agents that appear particularly promising as anti-inflammatory agents is presented below.

Fish Oils (EPA and Docosahexaenoic Acid)

Fish oil supplements derived from cold-water fish, generally herring, mackerel, salmon, bluefish, and tuna, are rich in EPA and docosahexaenoic acid (DHA). Long-chain w-3 fatty acids are rapidly incorporated into cell membrane phospholipids, where they influence cell metabolism. In addition to modulating eicosanoid synthesis, they alter cell membrane fluidity to produce subtle changes in receptor function, alterations in cell-signaling mechanisms, and regulation of gene expression.¹³⁴ EPA, and to a lesser extent DHA, antagonize AA via several mechanisms: (1) they sup-

plant AA in membrane phospholipids, (2) they inhibit the synthesis of AA from linoleic acid via their greater affinity for desaturase enzymes, and (3) they compete with AA for active sites on LOXs and COXs.¹³³ This competition limits the synthesis of pro-inflammatory prostanoids and LTs,¹⁹⁰ particularly as the LOX and COX by-products of EPA do not increase cancer cell proliferation.⁹² Decreased synthesis of PGE2 and/or LTB4 is observed following inclusion of flax or fish oil in the diet.¹⁹¹ Fish oils have been shown to selectively inhibit COX-2—without affecting COX-1—in a dose-dependent manner *in vitro*¹⁹² and *in vivo*.^{193,194} EPA at 1 to 2 μM in culture reduces the production of LTB4¹⁹⁵ and 5-HETE.¹⁹⁶ In addition, fish oil supplements markedly inhibit the synthesis of cytokines TNF- α and IL-1 in humans.¹⁹⁷ More than 20 human clinical trials have documented the anti-inflammatory effects of omega-3 fatty acid supplementation, primarily in patients with rheumatic disorders.¹³⁴ None of these studies have specifically addressed inflammatory events in cancer patients, although some research does support the benefit of fish oil supplements in cancer patients.

With regard to the potential of omega-3 fish oils to inhibit cancer proliferation and progression, a large number of *in vitro* and animal studies have been published. A majority of cell culture studies report that ω -3 fatty acids inhibit proliferation or invasion, prompt cell cycle arrest or apoptosis, or induce differentiation of cancer cells.^{141,198-202} Some *in vitro* and *in vivo* research also suggests that fish oils may have antiangiogenic properties.²⁰³⁻²⁰⁶

A large number of animal studies also report that ω -3 fatty acids, particularly EPA, produce antitumor effects. In studies of human tumors transplanted to mice, fish oil as 10% to 20% of the diet retards the growth of almost every type of cancer studied, including prostate,²⁰⁷ breast,^{138,208-211} lung,^{212,213} and colon carcinomas.²¹⁴⁻²¹⁶ A fish oil concentrate (providing 51% EPA, 35% DHA, and 7% other fatty acids) completely blocked the growth of preexisting cancers in rats following a 6-week treatment, including a 63% reduction in the size of the largest tumors.²¹⁷ Fish oil supplementation significantly inhibits the development and severity of lung metastases in mice implanted with highly metastatic colon carcinoma²¹⁸ or MDA-MB-435 human breast cancer cells.²¹⁰ In both studies, linoleic acid stimulated tumor growth and metastasis. Survival time is prolonged in mice bearing myeloid leukemia cells fed a diet rich in fish oil.²¹⁹

A limited number of studies on fish oil have been conducted in human cancer patients, primarily focusing on immunomodulation and anticachectic effects. Advanced pancreatic cancer patients supplemented with fish oil (2 g EPA, 1 g DHA daily for 4 weeks) achieved a stabilization of acute-phase protein response

markers of inflammation: C-reactive protein (CRP), ceruloplasmin, and fibrinogen.²²⁰ Fish oil supplements have also demonstrated anticachectic effects in patients with pancreatic cancer.²²¹⁻²²³ Supplementation with fish oil (18 g/day over a 40-day period) significantly increased T-helper/T-suppressor cell ratio in cancer patients with solid tumors.²²⁴ A randomized controlled trial of fish oil supplementation (18 g/day) in 60 patients with generalized malignancy showed significantly improved ratio of T-helper to T-suppressor cells and prolonged survival in patients taking fatty acid supplementation compared to those on placebo.²²⁵

The application of fish oils as an adjunct to conventional treatments may also prove useful, as indicated by preclinical studies. Omega-3 oils increase the cytotoxic efficacy of chemotherapy *in vitro*²²⁶⁻²²⁹ and *in vivo*.²³⁰⁻²³³ One mechanism of action underlying this effect is increased drug delivery across tumor cell membranes.²²⁶ EPA and DHA (15 to 45 μM) increase radiation-induced cell kill in a rat astrocytoma cell line,²³⁴ suggesting the potential to increase the therapeutic efficacy of radiation in the treatment of gliomas.

The high doses (e.g., 10% to 20% of diet) of fish oil used in some animal studies would have a human equivalent of 120 to 240 g per day. At excessive doses, the primary mechanism underlying tumor inhibition is likely increased lipid peroxidation and not solely eicosanoid modulation. Although some of these studies have correlated the antiproliferative effect of fish oils with increased lipid peroxidation,^{208,235-237} the application of this approach may be limited as separate research links increased oxidation with cancer cell proliferation and tumor progression,²³⁸ apparently by increasing cell mutation and altering cell signaling in ways favorable to cancer cells. Of note, moderate doses of EPA/DHA have also been reported to inhibit tumor growth and/or reduce metastasis in animals.^{183,210,239} These studies have employed doses of 1% to 2% of the diet (human equivalent 12 to 24 g per day). A human trial also showed favorable results with moderate doses of fish oil. In a retrospective study of 405 patients treated with stereotactic radiotherapy for metastatic brain lesions, supplementation with fish oil (3 g/day) and the bioflavonoid silymarin (200 mg/day), beginning 2 weeks posttreatment, resulted in a 64% increase in survival duration and significant decrease in radionecrosis compared to unsupplemented patients.²⁴⁰

Dose recommendations for fish oils among nutrition-oriented practitioners vary widely, and further research is needed to characterize the optimum dose of fish oil in cancer patients. Research on inflammatory conditions reports effective oral doses ranging from 1.2 to 4.6 g/day of fish oil (600 to 2300 mg/day EPA + DHA). Moderate doses of omega-3 PUFAs (540 mg EPA and 360 mg DHA) favorably alter tissue fatty

acid profiles in cancer patients,²⁴¹ and a dose providing 2.1 g EPA and 1.9 g DHA reduced PGE2 production in intestinal cells of healthy subjects.²⁴²

The tolerable upper limit for a fish oil concentrate offering 63% EPA + DHA in human cancer patients is reported to be 0.3 g/kg body weight (e.g., for a 70-kg patient, the tolerable dose is 21 g/day, providing 13 g EPA + DHA).²⁴³ Dose-limiting side effects in this study were gastrointestinal in origin, mainly diarrhea and esophageal or gastric irritation. Taking fish oil supplements with meals, as well as coadministration of lipase digestive enzyme, can limit side effects in some patients taking high-dose fish oil supplements. In addition, it is essential to ensure high-quality fish oil products which are stabilized and free of aldehydes and lipid peroxides. When taking fish oil supplements, increased vitamin E intake is essential to protect against elevated lipid peroxidation and depletion of antioxidants, particularly tocopherols. Lipid peroxidation can be monitored with lab assessment (such as urine malondialdehyde levels).

Despite concerns with regard to excessive blood thinning or interaction with anticoagulant medications, a controlled, randomized, double-blinded human clinical trial found no interference on the anticoagulant status of patients receiving chronic warfarin therapy with fish oil supplementation in doses of 3 to 6 g/day.²⁴⁴

Green-Lipped Mussel Extract

Marine lipid extracts from *Perna canaliculus* Martin (Mytilidae), the New Zealand green-lipped mussel, also deserve attention for their potent anti-inflammatory effects. In animal models, *P. canaliculus* extracts (PCEs) are significantly more effective at reducing inflammation than aspirin, ibuprofen, or indomethacin.^{245,246} PCE produces a dose-dependent reduction in LBT4, 5-HETE, and 12-HETE in vitro, with an inhibitory concentration (IC₅₀) between 20 and 50 µg/ml.²⁴⁷ The concentration is easily achieved clinically.

Lipid-rich extracts of stabilized PCE have recently become commercially available. They are safe and effective in the management of inflammatory conditions and free of significant side effects. Unlike NSAIDs, they offer a gastroprotective effect. To date, the effects of these extracts have not been studied in cancer.

Antioxidant Nutrients

There is a reciprocal relationship between antioxidants and inflammation. The magnitude of inflammation plays an important role in regulating circulating concentrations of vitamin antioxidants in cancer patients, and antioxidants offer anti-inflammatory effects. High levels of inflammation are known to deplete

host antioxidant stores, and anti-inflammatory agents have been demonstrated to increase antioxidant reserves in cancer patients.²⁴⁸ Whereas either a selective COX-2 inhibitor (SC58125) or antioxidant as a single agent is capable of reducing colorectal tumor growth in vivo, combined treatment demonstrates potent additive effects, markedly decreasing prostaglandin levels and resulting in tumor regression.²⁴⁹ Whereas selective COX-2 inhibitors block COX-2 catalytic activity, antioxidants decrease COX-2 expression at the transcriptional level.²⁴⁹

A large number of substances have antioxidant activities, including vitamins A, C, and E, selenium, zinc, carotenoids, flavonoids, coenzyme Q10, N-acetyl cysteine, lipoic acid, and numerous other compounds. Accordingly, a thorough examination of the role of these compounds in the inflammatory events falls outside the scope of this article. Here, we limit our discussion to vitamins A and E.

Vitamin A

Retinoids, including all-trans retinoic acid (RA), 9-cis-RA, 13-cis-RA, and retinyl acetate, suppress EGF-mediated induction of COX-2 mRNA and protein in vitro and inhibit the synthesis of PGE2.^{60,250} Treatment of squamous carcinoma cells with retinoid (9-cis-retinoic acid) suppressed COX-2 expression and PGE2 biosynthesis in concentration-dependent fashion and significantly inhibited cell growth.²⁵¹ These findings suggest that the combination of COX-2 inhibitors with retinoids may offer synergistic effects. Hypothetically, the therapeutic efficacy of 13-cis-retinoic acid (Accutane) in oncology may also be increased with concomitant administration of COX-2 inhibitors or natural anti-inflammatory protocols. This hypothesis warrants investigation.

Vitamin E

Vitamin E is the primary antioxidant responsible for the protection of cell membrane lipids. Alpha tocopherol inhibits the activity of phospholipase A2 in vitro and in vivo.²⁵² Alpha tocopherol offers anti-inflammatory effects in in vitro and animal studies.²⁵³ Macrophages from animals fed vitamin E deficient diets secrete significantly higher levels of PGE2, TXB2, LTB4, and 5-HETE.²⁵⁴ Oral administration of tocopherol decreases production of 5-HETE by rat leukocytes.²⁵⁵ Whereas a 1987 clinical trial of vitamin E supplementation failed to demonstrate a reduction in mucosal release of PGE2 and LTB4 in patients with ulcerative colitis,²⁵⁶ a recent study of diabetic patients at risk for cardiovascular disease found that vitamin E supplementation reduces inflammatory markers.²⁵⁷ A plausible explanation for the varied findings of these and other studies evaluating antioxidants in humans may

be the failure to measure the functional activity of the nutrient studied. It is inappropriate to derive conclusions from studies that standardize the dose, or even blood level, of an antioxidant nutrient administered. Rather, the baseline oxidative status of the individuals must be accounted for and individually tailored doses of antioxidants provided to achieve a standardized target level of oxidative stress, based on laboratory testing. Furthermore, antioxidant activity cannot be conferred by a single nutrient but only through the coordinated activities of a network of vitamins, minerals, and phytochemicals. Recognition of the “antioxidant network” may demand the modification of single-agent research from which conclusions about antioxidants have inappropriately been drawn.

The form of tocopherol selected may also be of particular importance. One study reported that gamma tocopherol reduces PGE₂ synthesis in macrophages and epithelial cells whereas alpha tocopherol has little or no effect on PGE₂ synthesis.²⁵⁸ Many questions remain with regard to the impact of vitamin E on arachidonate metabolism and inflammatory events in humans, and further research is needed.

Botanical Anti-Inflammatory Agents

Numerous botanical agents are capable of modulating the inflammatory response in humans. Phytomedicines are available that offer not only COX-inhibiting but also LOX-inhibiting activity, and thereby reduce the production of PGE₂, LTB₂, 5-HETE, 12-HETE, and other inflammatory compounds, which have been demonstrated to play significant roles in tumor viability, cell proliferation, angiogenesis, invasion, and metastasis. Each of the anti-inflammatory botanicals selected for review here has some *in vitro* and *in vivo* research on its promise as an anticancer agent. Unfortunately, none of the research to date has investigated the anticancer activities of these herbs in relation to their COX- or LOX-inhibiting effects. This observation provides a direction for future research.

The side effect profile of these botanical agents is exceedingly favorable in comparison to NSAIDs and COX-2 inhibitors. Despite considerable gaps in the research, the demonstrated anti-inflammatory actions and potential anticancer properties of these botanicals—considered together with their safety in human consumption—make a compelling case for their use in integrative cancer therapies. In clinical practice, the combination of several botanical agents, often at slightly reduced doses individually, may achieve considerable synergistic effects.

Boswellia

Boswellia [*Boswellia serrata* Roxb. Burseraceae] is an Ayurvedic remedy (salai guggal) with a long history of

use in rheumatic conditions. The resinous extract is used, with primary efficacy deriving from its boswellic acids, well-tolerated pentacyclic triterpenes. Boswellic acids have been demonstrated to be highly selective and potent inhibitors of 5-LOX.²⁵⁹⁻²⁶⁴

Boswellic acids promote differentiation in various leukemia cell lines^{265,266} and, in low micromolar concentrations, induce apoptosis in glioma cell lines, independent of p53 status.²⁶⁷ Boswellic acids may be particularly appealing anti-inflammatory agents for adjunct use in human brain tumors. They markedly inhibit glioma growth in animal experiments and increase survival time.^{268,269} Two uncontrolled human trials of high-dose oral boswellic acids in patients with intracranial tumors showed effective reduction of tumor-associated edema and marked improvement in clinical symptoms in as little as 7 days.^{270,271} No major side effects were reported in either study, although a small percentage of patients taking boswellia report gastrointestinal upset (which can often be eliminated by reducing the dose or taking the product with meals).

The recommended dose is based on the concentration of boswellic acids in the extract and is approximately 30 to 50 mg/kg/day. Crude preparations of boswellia typically contain 43% boswellic acids, with some commercial sources offering up to 65% boswellic acids.

Bromelain

Bromelain refers to the mixture of sulfur-containing proteases obtained from the stem of the pineapple plant, *Ananas comosus* (L.) Merr. (Bromeliaceae). Since its introduction in 1957, more than 400 scientific papers have been published on its therapeutic applications. A review article²⁷² documents the following actions for bromelain: (1) interference with growth of malignant cells, (2) inhibition of platelet aggregation, (3) fibrinolytic activity, and (4) anti-inflammatory actions. Historically, bromelain has been used to reduce inflammation in cases of arthritis, sports injury, trauma, and postsurgical swelling. Bromelain selectively stimulates the production of PGE₁²⁷³ and inhibits the synthesis of pro-inflammatory PGE₂ in a dose-dependent manner.²⁷⁴ Bromelain's inhibition of PGE₂ biosynthesis exceeds the anti-inflammatory effects of prednisone, which requires a 10-fold greater dose to achieve the same effect in rats.²⁷⁴ The anti-inflammatory actions of bromelain in postsurgically treated patients have been demonstrated in a double-blind crossover trial.²⁷⁵

Bromelain significantly decreased metastases of Lewis lung cancer in mice.^{276,277} Two uncontrolled trials from the 1970s with oral bromelain (doses ranging from 600 to 2400 mg/day) reported positive results, including subjective evidence of tumor regressions of ovarian and breast cancers and their metastases.^{278,279}

Bromelain stimulates immune response in breast cancer patients,²⁸⁰ which may also in part explain its proposed antitumor activity.

Typical oral dose ranges from 250 to 750 mg, TID, on an empty stomach, of product standardized to provide 1800 to 2400 mcu/g (1.5 gdu = 1.0 mcu). Bromelain enhances the absorption of drugs taken concurrently.²⁷² Although bromelain is reported to have blood-thinning and antithrombotic effects in animal studies,²⁸¹ human research has not confirmed this finding or substantiated the concern that bromelain may interact with oral anticoagulants.^{280,282}

Curcumin

Curcumin, diferuloylmethane, is the yellow pigment and active component of turmeric, *Curcuma longa* L. (Zingiberaceae). A small molecular weight compound, curcumin constitutes 1% to 5% of the content of turmeric. It has a long history of safe use in Ayurvedic medicine, an indigenous system of medicine from India, particularly in the treatment of inflammatory disorders. In addition to its anti-inflammatory properties, curcumin is a potent antioxidant, stronger than vitamin E in preventing lipid peroxidation in vitro.^{283,284}

Curcumin inhibits both COX and LOX, reducing the synthesis of PGE₂, LTB₄, and 5-HETE in vitro and in vivo.²⁸⁵⁻²⁹² Numerous studies confirm curcumin's anti-inflammatory effect in vivo. Animals with colon cancer fed curcumin show a 50% decrease in phospholipase A₂ activity and nearly 40% reduction in the levels of PGE₂ in colonic mucosa and tumor.²⁹³ Patients with colorectal cancer fed an oral preparation of curcuminoids (36 to 180 mg curcuminoids per day) exhibited a dose-dependent reduction in COX-2 expression and PGE₂ production.²⁹⁴ Patients with postoperative inflammation achieved a similar anti-inflammatory response with oral curcumin (1200 mg/day) compared to NSAID administration.²⁹⁵ In patients with rheumatoid arthritis, curcumin (1200 mg/day) offers anti-inflammatory effects, without side effects, comparable to phenylbutazone (300 mg/day).²⁹⁶

Interest in the anticancer actions of curcumin is considerable, and research efforts are expanding in this area. Curcumin (3 to 20 μ M, occasionally up to 50 μ M) exhibits antiproliferative effects in vitro in a variety of human cancer cell lines, including estrogen-dependent and estrogen-independent breast,²⁹⁷ prostate (both hormone-dependent and hormone-independent cell lines),²⁹⁸ colon,^{299,300} oral squamous carcinoma,³⁰¹ melanoma,³⁰² lymphoma,³⁰³ and leukemia^{304,305} cell lines.

Curcumin exerts various influences on the pathophysiology of malignant cells. In vitro studies on various cell lines have shown that curcumin promotes cell

cycle arrest^{299,306} and induces apoptosis.^{298,304,307,308} Limited in vitro and in vivo evidence suggests curcumin may also have antiangiogenic effects.³⁰⁹⁻³¹¹ In animal studies, curcumin increased the life span of rodents with transplanted tumors, inhibiting tumor growth and impeding metastasis.^{312,313}

Preliminary evidence suggests curcumin may selectively enhance the cytotoxicity of chemotherapy while offering protective effects against various side effects. In animal experiments, very high doses of curcumin protect against bleomycin-induced and cyclophosphamide-induced pulmonary fibrosis and deter chemotherapy-induced increases in biomarkers of the inflammatory response.³¹⁴⁻³¹⁶ In vivo protection against Adriamycin-induced nephrotoxicity has also been demonstrated.³¹⁷ When given orally with cisplatin, curcumin (28 mg/kg) reduced progression of fibrosarcoma in rats better than cisplatin alone.³¹⁸ The human equivalent dose for this latter study is about 450 mg/day.³¹⁹

In the only human study to date, topical curcumin ointment provided symptomatic relief for patients with ulcerating oral or cutaneous squamous cell carcinomas who had previously failed to respond to standard treatments.³²⁰

Human studies on curcumin's anti-inflammatory effect have generally used a dose of 750 to 1500 mg/day. Extrapolating from animal studies, the oral dose of curcumin that might be expected to offer a benefit in cancer is 1500 mg/day or slightly greater, as tolerated. Curcumin is exceedingly safe and nontoxic, even at very high concentrations. Doses exceeding 2.5 g/kg fed to rats, guinea pigs, and monkeys confer no evidence of harm or genetic damage.³²¹ Curcumin is contraindicated in individuals with biliary duct obstruction.³²²

Quercetin

A ubiquitous flavonoid in plants, quercetin is the major bioflavonoid in the human diet. Quercetin interferes with many steps in eicosanoid metabolism. It inhibits phospholipase A₂ activity³²³ and blocks both the LOX³²⁴ and COX³²⁵ pathways of AA metabolism. At micromolar concentrations (≤ 15 -40 μ M), quercetin inhibits COX-2 and LOX-5 activity.^{325,326} It is also a potent inhibitor of TGF- α induced COX-2 activity.³²⁷

A review article on the anticancer actions of quercetin suggests that the flavonoid may have significant potential as an anticancer agent.³²⁸ The reported in vitro effects of quercetin include down-regulation of mutant p53 protein, cell cycle arrest at G₁, tyrosine kinase inhibition, inhibition of heat shock proteins, and suppression of ras protein expression. Documented in vivo activities reported in this review article include inhibition of tyrosine kinase in cancer patients, inhibition of

tumor growth, and increased life span in tumor-bearing animals. In experimental models, quercetin has demonstrated significant antitumor activity against a wide range of cancers, including brain tumors,³²⁹ squamous cell carcinomas,³³⁰ non-small cell lung cancers,³³¹ and cancers of the breast,³³² ovary,³³³ bladder,³³⁴ stomach,³³⁵ and colon.^{336,337} In vitro and in vivo studies on various cancer cell lines show quercetin potentiates the therapeutic efficacy of cisplatin, adriamycin, busulphan, and cyclophosphamide, and decreases resistance to gemcitabine and topotecan.³²⁸

For anticancer activity, doses of quercetin reportedly must achieve 10 μM or greater serum concentrations, and a suggested oral dose to achieve this concentration is 1500 mg/day.³²⁸ Quercetin has little toxicity when administered orally or intravenously, even in large doses, and is well tolerated in humans.

Additional Botanical Agents to Consider

Many additional herbs have anti-inflammatory effects and deserve consideration as adjuncts in cancer treatment or chemoprevention. These compounds have growing bodies of literature investigating their anticancer potential. Botanical compounds with documented ability to inhibit COX-2 and/or reduce PGE2 synthesis in experimental models are *Aloe vera* (L.) Burm.f. (Liliaceae)³³⁸; epigallocatechin gallate extracts of green tea, *Camellia sinensis* Kuntze (Theaceae)³³⁹; resveratrol³⁴⁰; and licorice, *Glycyrrhiza glabra* L. (Fabaceae).³⁴¹ *Allium* species (e.g., garlic) derived ajoene inhibits COX-2 enzyme activity in vitro and reduces the release of PGE2 in a dose-dependent manner.³⁴² *Scutellaria baicalensis* Georgi (Lamiaceae) contains baicalein (a trihydroxyflavone), which is a selective inhibitor of 5-LOX and 12-LOX in micromolar concentrations.^{343,344} Herbs with traditional use as anti-inflammatories awaiting research documenting their eicosanoid-modulating effects include bilberry, *Vaccinium myrtillus* L. (Ericaceae); feverfew, *Tanacetum parthenium* Sch.-Bip. (Asteraceae); pine bark and grape seed extracts; devil's claw, *Harpagophytum procumbens* DC. (Pedaliaceae); picrorrhiza *Picrorrhiza kurroa* Benth. (Scrophulariaceae); hops, *Humulus lupulus* L. (Cannabaceae); Asian ginseng, *Panax ginseng* C.A. Meyer (Araliaceae); and milk thistle, *Silybum marianum* Gaertn. (Asteraceae).

Lab Assessments to Monitor Inflammation

In using complementary strategies such as dietary, nutritional, and botanical support, laboratory assessments are imperative to monitor the intervention and to guide individualized tailoring of protocol. Direct measurements of COX-2 and LOX activities, and quan-

tifications of PGE2, LTB4, 5-HETE, and 12-HETE, would be ideal but are not readily available. However, the following lab assessments may prove both practical and worthwhile.

Fatty Acid Analysis

Red blood cell fatty acid analysis can provide valuable insight into imbalances in eicosanoid substrates and alterations in their metabolism. The results can be particularly helpful in assisting the practitioner to recommend appropriate dietary modifications and to monitor compliance with the diet.

Interleukin-6

Serum measurements of IL-6 may be useful, as this cytokine up-regulates inflammation and also appears involved in cachexia. In patients with colorectal cancer, those with stage III-IV disease had higher levels of serum IL-6 levels than those with stage I-II disease. In addition, 5-year survival was greater in patients with IL-6 less than 10 pg/mL compared to cases in which IL-6 concentration was greater than 10 pg/mL.³⁴⁵ In lung cancer patients, serum IL-6 is frequently elevated, and the elevation is associated with poorer nutritional status and shorter survival time.³⁴⁶

Acute Phase Proteins

Acute phase protein response (APPR) markers are an innovative and invaluable means of monitoring inflammatory status in cancer patients. During the inflammatory response, CRP, ceruloplasmin, and fibrinogen concentrations increase whereas levels of albumin and transferrin decrease. With disease progression in cancer patients, APPR markers also progress: CRP, ceruloplasmin, and fibrinogen increase whereas albumin and transferrin decrease.²²⁰

CRP appears particularly promising for use in this application. CRP is an acute phase protein formed by hepatic cells via cytokine stimulation, particularly IL-6. CRP levels increase very rapidly in response to trauma, inflammation, and infection; they decrease rapidly with resolution of the condition.

CRP levels have been demonstrated to be elevated in cancer patients. Compared to healthy controls, serum levels of CRP are significantly increased in patients with gastrointestinal cancer²⁴⁸ and advanced pancreatic cancer.³⁴⁷

Tumor recurrence following treatment is associated with a statistically significant elevation of CRP concentration in patients with head-and-neck cancer³⁴⁸ and early stage colorectal cancers.³⁴⁹ Colorectal cancer patients with elevated preoperative serum CRP had significantly greater incidence of hepatic metastases, peritonitis carcinomatosa, lymph node involvement,

and intravascular invasion than patients with negative CRP.³⁵⁰

Moreover, elevated CRP correlates with poorer prognosis and decreased survival in cancer patients with unresectable pancreatic cancer,³⁵¹ multiple myeloma,³⁵² renal cell carcinoma,³⁵³ and advanced colorectal cancer.^{350,354,355} Two prospective studies have shown a 3-fold increase in survival duration for cancer patients without elevated CRP concentrations compared to those with elevated values. In unresectable pancreatic cancer patients, median survival of those with acute-phase protein response (CRP > 10 mg/L) was 66 days compared to 222 days for those with no acute-phase protein response.³⁵¹ In patients with advanced gastrointestinal cancers, those with elevated CRP values had a reduced survival duration (median survival: 136 days) compared to patients without CRP elevations (median survival: 466 days).³⁵⁶ This association was independent of significant weight loss (median: 16.6% weight loss).

Treatment with anti-inflammatory agents can reduce CRP levels in cancer patients. For example, ibuprofen (1200 mg/d, po, q 8-11 days) reduces circulating concentrations of CRP, IL-6, and cortisol, and also lowers elevated platelet counts in patients with gastrointestinal cancers.³⁵⁷

Technological advances have yielded a newer version of the test, the high-sensitivity CRP, which has superior sensitivity. CRP is elevated in inflammatory diseases and bacterial infection (pneumonia, pancreatitis, pelvic inflammatory disease, urinary tract infection, appendicitis, meningitis, etc.).³⁵⁸ Tissue injury—such as accompanies surgery or radiotherapy—increases CRP levels.^{359,360} Liver disease may also influence CRP. Consideration of these confounding variables must be made in interpreting CRP values in cancer patients.

Conclusion

Pharmaceutical COX-2 inhibitors hold promise as adjunctive therapies in the prevention and treatment of cancer. A handful of NCI-sponsored phase I and II trials of Celebrex[®] in cancer chemoprevention and treatment are currently under way. Clinical investigations need to determine the dose schedule and duration of treatment that afford optimum benefit. Inflammation follows a circadian rhythm, and the timing of daily administration of COX-2 inhibitors may prove to be an important variable. For example, administration of celecoxib in MCF-7 tumor bearing mice achieved 60% growth inhibition when given 7 hours after light onset but only 22% inhibition when administered 3 hours after light onset.³⁸ Examinations of circadian effects in humans taking COX-2 inhibitors may be advantageous. Accurate identification of those cancer patients most likely to benefit from COX-2 inhibitors is also needed.

Although in vitro and animal studies completed to date lend substantial credibility to the hypothesis that natural COX-2 and 5-LOX inhibitors may enhance cancer therapy, substantial investigations remain to be completed, culminating in well-designed human trials. Today's cancer patients—many facing dire prognoses and an urgency that does not afford waiting for the final results of clinical trials on complementary approaches—must evaluate the data currently available and, together with the guidance a qualified oncologist and an experienced practitioner of integrative medicine, make informed treatment choices. From the available data, it appears that these individuals have much to gain from the incorporation of natural anti-inflammatory strategies that pose little risk of adverse effect and offer reasonable promise of benefit. The outcome of these clinical choices needs to be carefully documented. And several directives for future research into natural anti-inflammatory protocols are clear. Natural agents should be screened for LOX- and COX-inhibiting effects. When natural agents are studied for anticancer properties, the contribution of COX or LOX inhibition should be examined. Optimal doses, as well as characterization of the synergistic effects of combinations, must be determined.

A weakness of much research to date is the failure to measure and control for the influence of eicosanoids other than the primary metabolite under investigation. For example, very few studies evaluating COX-2 (and PGE2) have accounted for the influence of LTs, thromboxanes, HETEs, and other compounds. Contradictory results observed in some of the research, such as studies that have shown that increased inflammation induces tumor regressions,³⁶¹ may ultimately be explained by the confounding influence of LTs, HETEs, TXs, isoprostanes, or other as yet undiscovered eicosanoids. Further discoveries in eicosanoid research are no doubt forthcoming, and following these, investigation of their potential roles in tumor physiopathology. Are there further isoforms of COX (COX-3, perhaps?), and what are their relationships to cancer? Beyond PGE2, what are the influences of other families of prostaglandins (e.g., PGF, PGD, PGI, etc.)? PGF2 alpha has been characterized as a potent pro-inflammatory prostaglandin and deserves evaluation. What are the influences on cancer of thromboxanes? What are the effects of the various isoforms of LOX and their LT metabolites (e.g., LTB5, LTB1)? What is the role of isoprostanes in cancer?

Many questions remain to be explored by future research on eicosanoid modulation in cancer therapy, including the following:

1. Which types of cancer cell growth are mediated preferentially by COX- vs LOX-derived eicosanoids?

2. Is there a synergistic inhibitory effect when both COX and LOX pathways are blocked?
3. Can natural anti-inflammatory protocols work as effectively as pharmaceutical COX-2 inhibitors (and LOX inhibitors, Zileuton[®], soon to enter the market)?
4. What are the best selection criteria for patients most likely to benefit from anti-inflammatory protocols? Can lab assessments of inflammation (e.g., elevated CRP, ceruloplasmin, IL-6) identify these patients?
5. Do natural anti-inflammatory agents synergize with pharmaceuticals? For example, can botanical LOX inhibitors enhance the effects of selective COX-2 inhibitors?
6. Which natural anti-inflammatory agents are best suited—and which are inappropriate—for combination with conventional treatments, such as surgery, radiation, and chemotherapy? Are immunotherapies potentiated or hindered by COX or LOX inhibition?
7. What are the interrelationships of eicosanoids and hormones, such as estradiol, progesterone, dehydroepiandrosterone, cortisol, and melatonin, in cancer?
8. Can other available drugs, perhaps HMGCoA reductase inhibitors, low-dose naltrexone, Accutane[®], tamoxifen, butyrate, or cardiac glycosides, potentiate the anticancer effects of COX-2 inhibitors or natural anti-inflammatory compounds?

Modern oncology is being challenged to broaden its focus to include molecular management of the patho-physiological events attending neoplasia. Inflammatory deregulation represents one of these events, which is particularly amenable to dietary, nutritional, and botanical modulation. The field of eicosanoid research in cancer prevention and treatment is in its adolescent years. Although still struggling through an awkward phase of self-discovery, it is imbued with great expectations. If these approaches can fulfill their expectations, cancer patients may one day be able to view their disease not as a death sentence but as a chronic condition requiring ongoing management, which may ultimately allow those afflicted to live out their natural life span.

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Editor's Note

This important review by Jeanne M. Wallace of the role of eicosanoids in stimulation of the growth of tumors,

and the potential for inhibiting their activities by inhibiting the action of lipoxygenase and cyclooxygenase (COX) enzymes, provides a scientific foundation for one of the most common strategies of integrative nutritional programs: the limitation of meat in the diet and its substitution with fish and other sources of omega-3 fatty acids. Wallace's exploration of the pharmacology of COX-2 inhibitors in various cancers is detailed and convincing, and she has done the integrative medicine community a real service in reviewing the potential use of natural COX-2 inhibitors. This pharmacology is truly where mechanism-based biology intersects directly with the therapeutic realities of both conventional and complementary/alternative treatment, and this article provides a solid basis for understanding COX-2 inhibitors for clinicians in both areas.