Minimizing the Cancer-Promotional Activity of Cox-2 as a Central Strategy in Cancer Prevention

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Abstract

A recent meta-analysis examining long-term mortality in subjects who participated in controlled studies evaluating the impact of daily aspirin on vascular risk, has concluded that aspirin confers substantial protection from cancer mortality. Remarkably, low-dose aspirin was as effective as higher-dose regimens; hence this protection may be achievable with minimal risk. There is reason to believe that this protection stems primarily from inhibition of cox-2 in pre-neoplastic lesions. Since safe aspirin regimens can only achieve a partial and transitory inhibition of cox-2, it may be feasible to complement the cancer-protective benefit of aspirin with other measures which decrease cox-2 expression or which limit the bioactivity of cox-2-derived PGE2. Oxidative stress boosts cox-2 expression by up-regulating activation of NF-kappaB and MAP kinases; NADPH oxidase activation may thus promote carcinogenesis by increasing cox-2 expression while also amplifying oxidant-mediated mutagenesis. A prospective cohort study has observed that relatively elevated serum bilirubin levels are associated with a marked reduction in subsequent cancer mortality; this may reflect bilirubin's physiological role as a potent inhibitor of NADPH oxidase. It may be feasible to mimic this protective effect by supplementing with spirulina, a rich source of a phycobilin which shares bilirubin's ability to inhibit NADPH oxidase. Ancillary antioxidant measures – phase 2 inducing phytochemicals, melatonin, N-acetylcysteine, and astaxanthin – may also aid cox-2 down-regulation. The cancer protection often associated with high-normal vitamin D status may be attributable, in part, to the ability of the activated vitamin D receptor to decrease cox-2 expression while promoting PGE2 catabolism and suppressing the expression of PGE2 receptors. Diets with a relatively low ratio of omega-6 to long-chain omega-3 fats may achieve cancer protection by antagonizing the production and bioactivity of PGE2. Growth factors such as IGF-I increase cox-2 expression by several complementary mechanisms; hence, decreased cox-2 activity may play a role in the remarkably low mortality from "Western" cancers enjoyed by Third World cultures in which systemic growth factor activity was minimized by quasi-vegan diets complemented by leanness and excellent muscle insulin sensitivity. Practical strategies for achieving a modest degree of calorie restriction may also have potential for down-regulating cox-2 expression while decreasing cancer risk. Soy isoflavones, linked to reduced cancer risk in Asian epidemiology, may suppress cox-2 induction by activating ERbeta. In aggregate, these considerations suggest that a comprehensive lifestyle strategy targeting cox-2 expression and bioactivity may have tremendous potential for cancer prevention.

Cancer Preventive Potential of Low-Dose Aspirin

Recent meta-analyses following up long-term health outcomes in subjects who participated in controlled trials of daily aspirin use for prevention of vascular events, have revealed that daily aspirin administration is associated with a marked reduction in cancer mortality; the largest impact was seen with adenocarcinomas, most notably those of gastrointestinal origin.[1, 2] At 20 years of follow-up, mortality from all solid cancers was 20% lower in those receiving aspirin; risk of death from adenocarcinomas was 34% lower. These findings are statistically robust, and are particularly astounding in light of the fact that these were intention-to-treat analyses (implying that subjects randomized to aspirin who were poorly compliant were nonetheless included as aspirin users), and a substantial proportion of subjects randomized to aspirin can be presumed to have discontinued aspirin use after the formal completion of their trials, which were not longer than 9 years. (It can also be presumed that some subjects randomized to placebo commenced aspirin use after trial completion, further reducing the power of the study to demonstrate benefit.) When analysis was restricted to subjects with duration of trial treatment over 7.5 years, the preventive effects were even more dramatic: deaths from all solid tumors were 31% lower, and deaths from gastrointestinal cancers were 59% lower. This suggests that continual use of daily aspirin throughout adulthood might well have an astoundingly positive impact on cancer mortality. Moreover, the meta-analyses concluded that a 75 mg daily dose was as protective as higher doses; hence, except in those individuals for which aspirin is outright contraindicated, marked protection could be achieved at a dose that would entail minimal risk for bleeding complications or other side effects. This is surely one of the most encouraging medical discoveries of recent decades.

It is probably reasonable to assume that aspirin's utility in this regard stems primarily from its ability to suppress production of cancer-promoting prostanoids by cox-2 in pre-cancerous lesions; thus, aspirin use has shown no impact on risk for colon adenocarcinomas that do not overexpress cox-2, or on risk for mortality in patients whose colon adenocarcinomas do not overexpress this enzyme.[3, 4] The cancer-promoting activity of cox-2-derived prostanoids, most notably PGE2, is thought to reflect autocrine or paracrine stimulation of prostaglandin receptors (the four subtypes EP1-EP4), which in many tissues inhibit apoptosis via cell-type-specific mechanisms such as increased Bcl-2 expression, decreased Bax or Bim expression, Bad phosphorylation, and Akt activation; stimulation of these receptors also often promotes proliferation, invasiveness, and angiogenesis, and inhibits the cancer-scavenging activity of cytotoxic T cells or NK cells.[5-15] The magnitude of protection observed in the recent meta-analyses is particularly remarkable in light of the fact that low-dose aspirin could only be expected to achieve partial and temporary inhibition of cox-2; since aspirin somewhat preferentially inhibits cox-1,[16] an aspirin regimen which achieved substantial sustained inhibition of cox-2 could be expected to suppress cox-1 activity at least as strongly, and hence would be associated with high risk for gastric ulceration and kidney damage. Indeed, low-dose aspirin appears to be notably more effective for preventing adenocarninomas of the proximal colon than those of the distal colon; Rothwell and colleagues note that, inasmuch as cox-2 expression tends to be higher in distal lesions, low-dose aspirin may have achieved insufficient inhibition of cox-2 activity in distal pre-cancerous lesions to provide optimal protection.[1]

Regulation of Cox-2 Expression

This latter point suggests the possibility that adjuvant measures which suppress the expression of either cox-2 or of prostaglandin receptors, or which limit the availability of arachidonic acid as a substrate for PGE2 synthesis, might complement the utility of low-dose aspirin for cancer prevention, enabling even greater protection to be achieved. Indeed, an examination of other measures suspected to be useful for cancer prevention reveals that many of them could be expected to decrease the cancer promotional activity of cox-2 in pre-cancerous lesions. Such measures include effective antioxidant strategies – of which spirulina-derived phycocyanobilin may have the most intriguing potential – as well as vitamin D, a diet with a low ratio of omega-6 fatty acids to long-chain omega-3 fatty acids, and dietary/lifestyle measures which could be expected to minimize systemic levels of insulin and free IGF-I.

Analysis of the promoter region of the human cox-2 gene reveals binding sites for NF-kappaB, C/EBP, AP-2, SP1, Ets-1, and a CRE motif.[17-19] Studies in various types of cells indicates that NF-kappaB can be a potent mediator of cox-2 transcription, and that the various MAP kinases – Erk1/2, JNK, and p38 – can also promote this transcription by boosting the activity of transcription factors and coactivators which target the cox-2 promoter.[19-26] It is well known that oxidative stress and various pro-inflammatory cytokines can promote activation of NF-kappaB and of the MAP kinases. Growth factors such as IGF-I or EGF also boost the expression of cox-2 mRNA; this may reflect stimulation of transcription via Erk1/2, as well as an increase in the half-life of cox-2 mRNA mediated by the PI3K-Akt pathway stimulated by most growth factors.[23, 27-30]

Bilirubin and Spirulina – Potential for Down-Regulating Cox-2 Expression

A number of studies show that oxidative stress can enhance cox-2 expression in many types of cells, acting via NF-kappaB and the MAP kinases.[25, 26, 31-38] NADPH oxidase complexes are a key source of oxidative stress, particularly in cells exposed to pro-inflammatory cytokines, and inhibition of NADPH oxidase has been shown to blunt cox-2 induction in many cell culture studies.[32-37, 39-44] The extent to which NADPH oxidase activation contributes to inflammatory carcinogenesis in humans, whether by cox-2 induction or other mechanisms, remains unclear. However, a very intriguing clue has emerged from epidemiology focusing on the physiological antioxidant bilirubin.

Whereas albumin-bound bilirubin functions as an important scavenging antioxidant in plasma, the intracellular concentration of free bilirubin is so low (low nanomolar range) that the important intracellular antioxidant activity of bilirubin cannot be credibly attributed to non-specific scavenging activity.[45] Recent studies reveal that, in intracellular concentrations achieved by heme-oxygenase-1 induction, bilirubin functions as a very potent inhibitor of NADPH oxidase complexes; the isoform specificity of this effect still requires clarification.[46-49] This discovery provides a satisfying rationale for recent epidemiology correlating increased serum bilirubin levels with reduced risk for vascular disorders, diabetes, and diabetic complications.[50-56]

Only one large prospective study to-date has examined the association between serum bilirubin levels and total cancer mortality. The Belgian Inter-University Research on Nutrition and Health study measured serum at baseline and correlated this with all-cause, cardiovascular, and cancer mortality during a 10-year follow-up in over 10,000 subjects of both sexes.[57] After adjustment for various covariants, subjects with

baseline bilirubin > 0.6 mg/dl, as contrasted with those with baseline bilirubin <0.2 mg/dl, were 58% less likely to have died of cancer over the next 10 years (RR=0.42; 95% CI 0.26-0.68). Cancer mortality in the intervening bilirubin strata was intermediate, and the inverse association of bilirubin level and cancer mortality had high statistical significance (p for trend = 0.004).

More recently, the association of baseline bilirubin with lung cancer incidence was evaluated in a huge British prospective cohort study (over half a million subjects, followed up over an average of 8 years).[58] Risk for lung cancer was found to decline monotonically with increasing bilirubin levels. Male risk for lung cancer in the tenth decile of bilirubin was 70% lower than that in the first decile, and 50% lower than that in the fifth decile; the findings in women were comparable. These findings are confounded somewhat by the fact that bilirubin levels tend to be slightly lower in current smokers, possibly owing to the oxidant effect of tobacco smoke. Nonetheless, a marked inverse association of bilirubin and lung cancer risk persisted after multivariate adjustments, including smoking status. These findings are highly consistent with a trend toward markedly lower lung cancer mortality in subjects with higher bilirubin status noted in the Belgian study, which presumably missed statistical significance owing to the modest number of cases involved.

Few other epidemiological studies to-date have examined the association between bilirubin and cancer risk. Two such studies have focused on colorectal cancer; a study employing data from the Third National Health and Nutrition Examination Survey found a large protective effect with increasing bilirubin; a 1-mg/dl increase in bilirubin was associated with a relative risk of 0.257 (95% CI 0,254-0.260).[59] Perplexingly, no such protection was observed when other researchers analyzed data from the First National Health and Nutrition Examination Survey.[60] The latter study has been criticized for failing to exclude subjects with elevated liver enzymes at baseline (in whom high bilirubin may have been a marker for liver disease), but the authors indicate that their conclusion was not altered when they did such an adjustment.[61, 62] Another pertinent study examined the association between common polymorphisms of the enzyme UGT1A1, responsible for conjugating bilirubin to glucuronic acid in the liver; reduced hepatic expression of this enzyme leads to increased circulating levels of free bilirubin. The analysis revealed that risk of head and neck cancer was significantly higher in subjects expressing the common high-expression allele of this gene.[63]

The possible impact of bilirubin on cancer risk can also be assessed by examining the role of heme oxygenase-1 (HO-1) in this regard. This gene likewise is polymorphic; an increase in the number of GT dinucleotide repeats in its promoter region is associated with less efficient expression in response to oxidative stress.[64] Oxidant-induced expression of HO-1 would presumably often help to quell this oxidative stress via generation of bilirubin.[49] However, HO-1 induction can be a two-edged sword in this regard, as it also releases free iron from catabolized heme. Subjects carrying decreased expression alleles of this gene have been reported to be at increased risk for esophageal squamous cell carcinoma, lung adenocarcinoma, postmenopausal breast cancer, and oral squamous cell carcinoma;[65-68] however, gastric cancer and melanoma were found to be more common in subjects carrying these alleles.[69, 70]

Clearly, more epidemiological research correlating bilirubin levels and polymorphisms of UGT1A1 and HO-1 with cancer risk are warranted. But the Belgian and British prospective studies provide strong reason to suspect that high-normal bilirubin levels may provide important protection from cancer. A

suppression of cox-2 induction in tissues exposed to inflammatory stimuli likely plays a key role in this effect. However, additional complementary mechanisms are likely at work. A moderate elevation of oxidative stress, produced by constitutive activation of NADPH oxidase, is observed in many cancers, and acts to promote survival and aggressiveness by up-regulating growth factor activities (via reversible inhibition of tyrosine phosphatases) and activation of NF-kappaB (which can oppose apoptosis by a variety of mechanism in addition to cox-2 induction).[71-73] Not unlikely, NADPH oxidase plays an analogous role in many pre-cancerous lesions, thereby aiding cancer promotion.[74, 75] Moreover, oxidants – notably peroxynitrite, and hydrogen peroxide in the presence of labile iron, can induce mutagenic damage.[76-79] Urinary 8-hydroxydeoxyguanosine is a marker for such damage, and the fact that serum ferritin levels tend to correlate directly, and transferrin receptor levels correlate inversely, with this marker in humans, suggests that iron-catalyzed oxidant damage to DNA makes an important contribution to spontaneous mutagenesis in humans.[80-82] Consistent with this possibility, a recent controlled study evaluating phlebotomy-induced iron depletion observed a significant reduction of cancer incidence in the iron-depleted group.[83] Hence, to the extent that elevated bilirubin levels can suppress the production of hydrogen peroxide and peroxynitrite in inflamed tissues, it may help to prevent inflammatory mutagenesis. (Keeping body iron stores relatively low should also be helpful in this regard. Diets low in heme iron – such as the vegan diet recommended below – tend to moderate body iron stores.)[84, 85]

These findings are of much more than theoretical interest, in light of recent evidence that oral administration of biliverdin can exert profound antioxidant effects in rodents that presumably are mediated by intracellular generation of bilirubin.[86] Moreover, whereas biliverdin is expensive to synthesize and is not readily available, the biliverdin derivative and homolog phycocyanobilin (PhyCB) constitutes about 0.6% by dry weight of the microalga spirulina. PhyCB is rapidly converted within cells to phycocyanorubin, a bilirubin homolog that appears to share its ability to inhibit to inhibit NADPH oxidase.[87, 88] This likely explains why oral administration of spirulina (or of phycocyanin, the spirulina protein which contains PhyCB as a chromophore) has been associated with profound and versatile anti-inflammatory and cytoprotective activity in rodent studies.[88-91] Hence, sufficient intakes of spirulina, or of PhyCB-enriched spirulina extracts, may have exciting practical potential for cancer prevention and for prevention and control of a range of other oxidant-driven pathologies.[88] The impact of spirulina/PhyCB on inflammatory carcinogenesis in rodents should receive further evaluation; inhibition of oral cancer and hepatic cancer with spirulina in rodents has already been reported.[92, 93]

Complementary Antioxidant Measures for Controlling Cox-2

Of course, PhyCB is not the only nutraceutical antioxidant which might have potential for suppressing cox-2 induction or oxidative mutagenesis. In particular, phase 2 inducers such as isothiocyanates, curcumin, epigallocatechin-gallate, and lipoic acid have been shown to decrease the expression of cox-2 in cell culture or rodent studies.[94-98] This may reflect induction of HO-1, but increased expression of other antioxidant enzymes and of glutathione could also be expected to blunt the impact of hydrogen peroxide on cell signaling as well as on inflammatory mutagenesis. Phase 2 inducers would also act to diminish cancer risk by promoting the conjugation and excretion of mutagenic electrophiles (i.e. activated carcinogens).[99, 100] Nocturnal melatonin administration has similar inductive effects that might prove comparably protective;[101] indeed, melatonin can blunt cox-2 induction in vitro, and has shown protective activity in rodent models of carcinogenesis.[102-107] Melatonin complements the efficacy of cox-2 inhibitors

in some of these studies. Moreover, a derangement of physiological melatonin release may contribute to the increased cancer risk observed in night-shift workers.[108-112] And N-acetylcysteine has the potential to complement the benefit of these inductive agents by potentiating their impact on cellular glutathione availability.[113-118] Ascorbic acid, like glutathione, is a key intracellular oxidant scavenger; in populations with poor baseline ascorbate status (in whom increased ascorbate intake can raise intracellular ascorbate levels[119]), vitamin C supplementation or an increase in consumption of ascorbate-rich fruits and vegetables may be protective.

The carotenoid astaxanthin is emerging as the most effective phytonutrient antioxidant for biomembranes, with considerably greater potential than vitamin E in this regard.[120] By protecting mitochondrial membranes from oxidative damage, this nutrient has the potential to moderate the contribution of stressed mitochondria to oxidant load.[121-123] Supplemental astaxanthin has been shown to suppress induction of cox-2 in the colon or rats treated with the carcinogen DMH, an effect associated with increased apoptosis in colonic mucosa.[124] In cell culture studies, it has blunted induction of cox-2 triggered by lipopolysaccharide or hyperglycemia.[125, 126] Moreover, in one of the first human supplementation studies with this nutrient, a reduction in a biomarker of DNA damage was observed.[127] Hence, astaxanthin may have worthwhile potential for cancer prevention and for prevention and control of other oxidant-driven disorders.[120]

Unfortunately, recent U.S. clinical studies focusing on prostate cancer risk have failed to realize hopes that supplemental selenium could provide protection from cancer; this may demonstrate that bolus carcinogen administration in rodents is a poor model for spontaneous carcinogenesis in humans.[128] However, baseline selenium nutrition in most Americans is relatively good, such that supplemental selenium has little impact on expression of glutathione peroxidase or other selenium-dependent antioxidant enzymes; selenium may well have greater potential for cancer prevention in populations where baseline selenium nutrition is poor owing to low selenium soil levels.[129, 130]

High-dose folate has intriguing antioxidant potential, owing to the fact that many tissues concentrate it against a gradient and reduce it to tetrahydrofolates which have versatile antioxidant activity.[131-133] In particular, tetrahydrofolates quench peroxynitrite-derived radicals, likely mediators of inflammatory mutagenesis; hence, the impact of high-dose folate on DNA integrity in oxidatively-stressed tissues merits attention. It is more doubtful whether folate could influence cox-2 expression. Folate status can also influence DNA repair, cell proliferation, and DNA methylation; the net impact of nutritional-dose folate supplementation on cancer risk is a matter of ongoing controversy, as available data are inconsistent. However, there is some reason to suspect that good folate status will counteract the increase in risk for breast and colon cancer associated with moderate alcohol consumption.[134, 135]

Squamous cell carcinomas – for which low-dose aspirin does not appear to be notably protective – tend to particularly common in disadvantaged populations consuming diets low in antioxidants such as vitamin C and flavonoids, and exposed to stressors such as tobacco smoke, alcohol, or betel nut that can induce oxidative stress.[136-143] Hence there is reason to suspect that increased oxidative stress may often play a mutational and promotional role in their induction. Consistent with this is evidence linking low-expression alleles of heme oxygenase-1 (one of whose key products is bilirubin) with increased risk for such cancers.[65, 68] Effective antioxidant measures may therefore complement mini-dose aspirin for cancer

prevention in the sense that they may provide protection from certain cancers not preventable with aspirin. Squamous cell carcinoma of the esophagus is said to be responsible for about one-sixth of total worldwide cancer mortality.[144]

Vitamin D Antagonizes Cox-2 Expression and Bioactivity

High-normal vitamin D status, usually reflecting adequate skin exposure to UV-rich sunlight, has been associated with decreased risk for various cancers in case-control and ecologic epidemiology.[145-147] Evidence that vitamin D provides protection from colorectal cancer is becoming overwhelming, but there are suggestive data that vitamin D may also provide protection from cancers of the breast, bladder, esophagus, gallbladder, stomach, ovary, renal, and the uterine endometrium.[148, 149] An ecologic analysis concluded that if all Americans achieved optimal exposure to UV light (and hence high vitamin D status), over 23,000 Americans annually would avoid premature death from cancer;[150] however, some prospective studies examining serum levels of 25-hydroxycholecalciferol have yielded more equivocal results.[151] Few placebo-controlled supplementation trials with vitamin D providing doses sufficiently high to reproduce the impact of optimal UV exposure have been done to date; however, one trial targeting postmenopausal women compared vitamin D (1100 IU) + calcium (1500 mg), calcium alone, and placebo over a 4 year period. When cancers that occurred over the first year were excluded (on the presumption that many of these were latently present when the trial began), relative risk for new non-skin cancer incidence in the vitamin D + calcium group was 0.232 (CI 0.09-0.60; $p<0.005$), whereas a trend toward reduced cancer n the calcium alone group did not achieve statistical significance. (A significant reduction in cancer risk was also seen in the vitamin D + calcium group when the first year cancers were included in the analysis: RR=0.402 (P=0.01).) This conclusion was however based on a total of only 50 cancer cases; results from large multi-center studies should be awaited eagerly.

These observations may reflect the fact that a high proportion of the epithelia which commonly give rise to cancer express 1-alpha-hydroxylase activity, and therefore are capable of autocrine production of calcitriol, the active hormone derived from circulating 25-hydroxycholecalciferol.[152, 153] Via interaction with vitamin D receptors – likewise commonly expressed in these tissues – calcitriol modulates gene expression in ways that tend to oppose carcinogenesis.

In particular, studies focusing on malignant or non-malignant breast or prostate cells, as well as colonic epithelium in vivo, have demonstrated that calcitriol, or less calcemic analogs thereof, can suppress cox-2 induction.[154-157] The basis of this effect is not entirely clear, although some studies have shown that calcitriol boosts the expression of MAP kinsase phosphatase 5, which opposes the activation of MAP kinases, notably p38.[158] But calcitriol also has the complementary ancillary effects of inducing the expression of 15-prostaglandin dehydrogenase – responsible for PGE2 catabolism - and suppressing the expression of prostaglandin receptors.[154, 157, 158] In other words, calcitriol has the potential to antagonize the bioactivity of prostaglandins, and thus presumably could complement the protection afforded by agents that inhibit cox-2 (such as aspirin) or suppress its expression. Indeed, Feldman and colleagues have demonstrated that, in prostate cancer cell lines that are moderately responsive to the anti-proliferative impact of calcitriol alone, this hormone can markedly potentiate the growth inhibitory effects of sub-optimal concentrations of NSAID drugs.[154]

It seems likely, however, that calcitriol can work in other, complementary ways to promote apoptosis or suppress proliferation in pre-cancerous tissues. For example, in many tissues, calcitriol or less calcemic analogs thereof have been shown to suppress NF-kappaB signaling, either by reducing expression of its components, by stabilizing or inducing IkappaB, or by acting within the nucleus to antagonize the transactivational activity of NF-kappaB.[159-171] (Up-regulation of NF-kappaB signaling by vitamin D activity has however been demonstrated in some contexts.[172]) A vitamin D-mediated increase in IGFBP-3 expression has also been reported in some tissues; IGFBP-3 counteracts the cancer-promotional activity of IGF-I, and also can exert direct antiproliferative effects in some cell lines.[169, 173-181] In some tissues the activated vitamin D receptor may boost the transcriptional activity of anticarcinogenic FOXO factors by facilitating their interaction with Sirt1.[182] And it has been suggested that vitamin D-mediated up-regulation of cadherin expression and tight junction formation could have an anti-promotional effect on epithelia.[183-185] No doubt the cancer-preventive effects of good vitamin D status will prove to be complex and cell type specific.

Importantly, there is recent evidence that supplemental intakes as high as 10,000 IU daily may be required to achieve in almost all subjects the serum levels of 25-hydroxycholecalciferol associated with optimal cancer protection in epidemiological studies.[186] Fortunately, intakes below 40,000 IU daily are likely to be safe.[186-188]

Long-Chain Omega-3s Limit PGE2 Production and Activity

Another feasible way to blunt the cancer-promoting activity of cox-2 is to limit its access to arachidonic acid, the precursor for the prostaglandins which mediate this activity. This can be achieved by minimizing the dietary intake of omega-6 fats relative to the intake of the long-chain omega-3s (EPA, DHA) found predominantly in fish oil; EPA can act as a competitive inhibitor of arachidonate binding to cox-2, and the PGE3 and other prostanoids derived from EPA tend to have anti-inflammatory rather than cancer-promoting activity. PGE3 fails to activate the EP2/EP4 receptors, and indeed acts as a competitive antagonist of PGE2 in this regard.[189] Epidemiological studies focusing on cancers of the breast, prostate, and colon have concluded that diets in which the ratio of omega-6 fats to long-chain omega-3 fats are relatively low, or a low omega-6/long-chain omega-3 ratio in blood or tissues, are associated with decreased risk.[190-200] A similar effect has been observed in rodent models of cancer promotion.[201-208] These considerations suggest that a “Mediterranean” profile of dietary fat – in which monounsaturates are the predominant fat, and intakes of long-chain omega-3s are significant – may be favorable for cancer prevention. It should be noted that, whereas supplemental fish oil reduced rectal cell proliferation (suspected to be a surrogate of colorectal cancer risk) in subjects consuming a low-diet, no such protection was noted when such supplementation was implemented in the context of diets high in omega-6.[209] Vegetarians should be aware that alpha-linolenic acid – the chief omega-3 in strict vegetarian diets – does not emerge as protective in some epidemiology, likely because humans convert it only inefficiently to the longer chain omega-3s that antagonize the cancer-promoting activity of cox-2.[199, 210-212] However, stearidonic acid (18:4n-3), which could be made in high yield by bioengineered plants, is more efficiently converted to longer chain fats, and may well have potential for cancer prevention.[213-216]

Lifestyle Modulates Cancer Risk via Systemic Growth Factor Activity and Cox-2 Expression

As noted above, growth factors can up-regulate cox-2 expression, both by activating Erk1/2, and by lengthening the half-life of cox-2 mRNA via an effect mediated by the PI3K/Akt pathway. In particular, IGF-I has been shown to have this effect in various cells lines. Insulin is also pertinent to this effect – either by a direct impact on insulin receptors, or by up-regulating systemic IGF-I activity by suppressing hepatic production of the IGF-I antagonist IGFBP-1.[217-219] The cancer prevention afforded by calorie restriction in rodent studies is mediated at least in part by a chronic down-regulation of circulating levels of insulin and free IGF-I,[220] and there is good reason to suspect that the far lower risks for many "Western" cancers enjoyed by various Third World cultures during the last century reflected the joint influence of quasi-vegan diets of modest protein content - which tend to down-regulate hepatic production of IGF-I owing to essential amino acid restriction - and of leanness and good muscle insulin sensitivity, which minimize diurnal insulin levels.[217-219, 221-224] Conceivably, increased levels of adiponectin, and modulation of mTOR activation and autocrine growth factor activity in cancer-prone tissues, might also contribute to the cancer protection afforded by such a lifestyle.[225] For example, increased autocrine production of IGF-II appears to mediate the promotional impact of dietary casein on hepatocarcinogenesis in rodents.[226]

A reduction in systemic insulin/IGF-I activity could be expected to decrease cancer risk by influencing both mutagenesis and promotion. Since mistakes are made whenever DNA is replicated, reduced proliferation in cancer-susceptible tissues would be expected to slow the rate at which stem cells accumulate heritable mutations. Moreover, insulin/IGF-I signaling may promote oxidant mutagenesis by suppressing FOXO3a-mediated transcription of the genes for catalase, the mitochondrial superoxide dismutase, and other antioxidant enzymes.[227-231] And growth factor activity works in a number of complementary ways (including cox-2 expression) to suppress apoptosis – thereby increasing the risk that pre-cancerous cells will survive long enough to acquire the mutations that turn them into full-fledged malignancies. Growth factor stimulation of Akt is particularly versatile in its suppressive impact on apoptosis.[232] A virtually obligate role for liver-derived systemic IGF-I in human carcinogenesis is suggested by the near absence of cancer in individuals who are homozygous for loss of function mutations in the gene for growth hormone receptor, in whom hepatic production of IGF-I is trivial.[233, 234] Vegans achieve a much less drastic suppression of hepatic IGF-I production.[223, 235]

With respect to breast cancer, low systemic growth factor activities may aid its prevention in part by delaying menarche and accelerating menopause.[236-238] This protective effect is compounded by the fact that serum estradiol levels are notably lower in rural Chinese women than in Western controls throughout life;[222, 239] premenopausally, this may reflect the fact that IGF-I activity potentiates ovarian estrogen synthesis.[240-242] This latter effect is not pertinent postmenopausally, when the lower estrogen levels and activity in Chinese women may be attributable to relative leanness and the increase in sex-hormone-binding globulin levels associated with good insulin sensitivity.[239] (Perhaps this explains why IGF-I levels correlate with breast cancer risk premenopausally but not postmenopausally in some Western studies.) It should be noted that early pregnancy may often contribute to reduced breast cancer risk in certain Third World societies, and multiple pregnancies diminish risk for ovarian cancer.

The cancer protection afforded by lifelong consumption of a plant-based diet, in conjunction with leanness and insulin sensitivity (which tend to be promoted by low-fat plant-based diets, owing in part to their low saturate/unsaturate ratio[243]) may be very substantial indeed. Figure 1 (derived from data

published by Ersnt Wynder and colleagues[244]) compares age-adjusted mortalities from various "Western" cancers in the populations of the U.S. and Japan, ca. 1955. Post-war Japan at this time was still a rather poor society; a national nutrition survey in 1950 determined that the Japanese were getting only about 6% of their calories from animal products (most of this from fish), as opposed to 78% of calories from grains.[245] Their omega-6 intake was quite low, so the modest amount of fat obtained from fish may have resulted in a low omega-6/omega-3 ratio. The Japanese at this time also tended to be quite lean, reflecting lifelong consumption of a diet of extremely low fat content; yet, unlike the Okinawans, they were not calorically restricted.[245] Note that age-adjusted death rates from cancers of the colon, prostate, breast, and ovary were on the order of 5-10-fold lower in Japan than in the U.S. at that time; mortality from pancreatic cancer, leukemias, and lymphomas was 3-4-fold lower in Japan.

But this phenomenon was by no means isolated to Japan; Western cancers were likewise comparatively rare in other Third World societies in which lean people ate plant-based diets. A paper by Hebert and colleagues provides data from the World Health Organization that provides estimated average daily food intakes for 59 countries, ca. 1979-1981; notably, these data estimate the percentage of daily calories provided by animal products in these countries.[246] The same paper provides age-adjusted prostate cancer mortality statistics in these same 59 countries for 1985-1989. The 6 countries on the list in which animal products were estimated to provide less than 10% of dietary calories (Egypt, Guatemala, Honduras, South Korea, Sri Lanka, and Thailand) subsequently experienced an average prostate cancer mortality rate of 1.96 per 100,000 males; in the 20 countries on the list which obtained over 1,000 kilocalories daily from animal products – including the U.S. and most Western European countries – this death rate averaged 29.91 per 100,000 males – 15-fold higher! (And the differential in *risk* for clinically significant prostate cancer was undoubtedly *higher* than that, as people in the poorer quasi-vegan countries would presumably have less access to sophisticated medical care, and thus would be less likely to achieve surgical cures of early stage cancer.)

With respect to breast cancer, consider the data that Kenneth Carroll compiled correlating average daily dietary animal fat intake (a rough surrogate for animal calorie intake) with age-adjusted breast cancer mortality in a number of countries, in the mid 1960s.[247] (See Chart 4 in this publication.) In the 6 countries where people were estimated to get no more than 20 g daily of fat from animal products, the breast cancer mortality averaged about 3.5 deaths per 100,000 females. In contrast, in the U.S., Canada, and Australia, this death rate averaged about 21 per 100,000. No doubt persistent epidemiologists could compile a number of similar examples. Are there any counterexamples of a society which consumed a predominantly plant-based diet, in which the people were typically lean and insulin sensitive – and Western cancer rates were high? This author has yet to encounter one.

Colin Campbell, in an analysis of data derived from the ecologic China Study (China-Oxford-Cornell Diet and Health Project), concluded that plasma cholesterol was the chief correlate of the range of Western cancers, as well as diabetes and coronary disease.[248] In quasi-vegan societies, such as those surveyed in this study, plasma cholesterol serves as a good marker for animal product consumption, since dietary cholesterol consumption reliably raises plasma cholesterol in vegans (whereas an increase of cholesterol consumption typically has minimal impact on the plasma cholesterol of omnivores).[249, 250] Campbell notes that, within the quasi-vegan provinces of rural China, "small intakes of foods of animal origin are associated with significant increases in plasma cholesterol concentrations, which are associated,

in turn, with significant increases in chronic degenerative disease mortality rates."[248] Once again, the regular consumption of animal products emerges as a major determinant of Western cancer risk. (However, increased red blood cell levels of DHA, presumably indicative of fish consumption, correlated negatively with Western disease risk in this population; this likely reflects the protection afforded by fish oil, rather than fish protein.)[251]

The promotional impact of high-quality protein on cancer risk has yet to win broad acceptance, in large measure because it fails to emerge in most Western epidemiology. This likely reflects the fact that the impact of essential amino acid status on the bioactivity of IGF-I and perhaps other growth factors plateaus once a certain minimal intake is reached. In the Nurses' Health Study, the *bottom* quintile of animal protein intake corresponds to 12% of calories.[252] In contrast, the populations surveyed by Campbell in the China Study got, on average, less than 1% of calories from animal protein, with total protein intake accounting for about 14% of calories.[222] Consideration should be given to the possibility that the *ratio* of nonessential to essential amino acids ingested has an impact on growth factor activities; a high intake of nonessential amino acids might decrease the effective availability of essential amino acids by promoting amino acid catabolism via glucagon.[243] Red meat does however emerge as a risk factor for cancer in much Western epidemiology; this could reflect the higher levels of heme iron and saturated fat in red meat. Campbell has repeatedly emphasized that exclusive reliance on Western epidemiological data bases can be counterproductive when those data bases fail to encompass lifestyles associated with marked health protection in other societies.[222]

The impact of obesity and metabolic syndrome on cancer risk – likely mediated by factors such as hyperinsulinemia, elevated free fatty acid flux, reduced adiponectin, and increased aromatase activity – is of course well documented in Western epidemiology, as is the protection associated with regular exercise. Third World populations at low risk for Western cancers tend to be quite lean by Western standards – the average BMI in the China Study population was 21, despite calorie intakes estimated to be about 30% higher than those of Americans of comparable body size.[253] A plant-based diet of moderate fat content, in conjunction with a physically active lifestyle, is inherently productive of leanness[243] – as repeatedly demonstrated by physicians who employ this strategy therapeutically.[254-256]

It is obvious on its face that it is vitally important to understand why age-adjusted death rates from many prominent Western cancers have been virtually an order of magnitude lower in many societies as compared to the West. Yet, with a few honorable exceptions, medical researchers have devoted relatively little attention to this crucial question. If some view the explanations attempted here as inadequate – where are the credible alternative hypotheses?

Nonetheless, it should be acknowledged that certain types of cancer – notably gastric, hepatic, bladder, and cervical – are often common in the Third World. But it seems likely that this reflects, not any inherent failing of a quasi-vegan diet, but rather poor hygiene, including poor food hygiene, that leads to chronic infections such as hepatitis, H. pylori, schistosomiasis, and papilloma virus, and to ingestion of mutagens produced by bacterial or mold contamination of improperly stored food. It is not accidental that gastric cancer rates tend to plunge when a society gains access to refrigeration.[257] The commonly noted ecological association between high-salt diets and gastric cancer may reflect, in part, the inadequacy of salt as a food preservative; however, heavily salted foods, even if uncontaminated, may play a pathogenic

role in gastric cancer induction, and their regular consumption should be discouraged.[258] In Mongolian gerbils, a diet extremely high in salt (10%) boosts the incidence of gastric cancer evoked by either concurrent H. pylori infection or administration of gastric carcinogens.[259-261] Intriguingly, a salty diet amplified the induction of cox-2 and iNOS in the gastric mucosa of gerbils infected with H. pylori.[262] Salt alone had no such inductive effect, a finding which accords nicely with cohort epidemiology concluding that dietary salt may represent a risk for gastric cancer only in individuals concurrently infected with H. pylori.[263] Not unlikely, cox-2 induction contributes to the nexus between other types of chronic infection and cancer risk.[264, 265]

Encouragingly, Campbell's analysis of the China Study noted that risks for both gastric and hepatic cancer trended lower in the more thoroughly vegan provinces; he supplemented this observation by demonstrating that low but nutritionally adequate protein intakes suppress induction of hepatic cancer by aflatoxin or hepatitis B in rats.[248, 266-268] Vegan diets, if hygienically stored and prepared, may be lower in mutagen load than omnivore diets. They do not contain heme iron, and also do not contain the mutagenic heterocyclic amines produced in flesh exposed to high heat.[269, 270] (These are made only in flesh foods, as creatine is an obligate precursor.) Moreover, vegan diets are devoid of animal fat, and thus tend to be lower in the fat-soluble xenobiotic compounds (some of which may be mutagenic) that accumulate in animal fat.[271, 272]

As noted above, diets of low variety deficient in antioxidant nutrients and phytochemicals may contribute importantly to high risks for various squamous cell carcinomas (especially esophageal) in certain regions of the Third World. Obviously, whole-food vegan diets of good variety can supply these protective nutrients in abundance.

Calorie Restriction Suppresses Cox-2 Expression

As noted, calorie restriction tends to prevent or postpone cancer in rodents, largely because of its impact on growth factor activities. The sirt1 induction associated with such diets could be expected to suppress NF-kappaB activation,[273-275] and thereby down-regulate cox-2 expression. Not surprisingly, calorie restriction has been reported to decrease cox-2 expression in rodents.[276-278] Although daily calorie restriction achieved by a strict accounting of calories is likely to prove impractical for all but a tiny percentage of people, potentially more feasible regimens such as modified alternate day fasting and carbohydrate-concentrated diets have been proposed as strategies for achieving a measure of calorie restriction in humans.[279-282]

Soy Isoflavones – Does ERbeta Activity Down-Regulate Cox-2?

A number of epidemiological studies have found that increased intakes of soyfoods or of soy isoflavones are associated with reduced risk for prostate, breast, and colorectal cancers – the chief causes of cancer mortality among non-smokers in the West.[283-291] Decreased risks for ovarian, endometrial, and gastric cancers have also been correlated with increased dietary soy.[292, 293] These findings are most consistent in East Asian studies, presumably reflecting habitual intakes of soy in East Asia that are higher and more physiologically meaningful; meta-analyses of pertinent East Asian studies observe a robust protective effect of soy (with the exception of colorectal cancer risk in men). These findings should be interpreted

cautiously, in light of the fact that a high soy intake may serve as a marker for a diet that is less Westernized.

Nonetheless, there are compelling theoretical grounds for suspecting that soy isoflavones may indeed be protective. Genistein can act as a pure agonist for both the alpha and beta isoforms of the estrogen receptor, but its affinity for the beta isoform is over an order of magnitude higher.[294, 295] Physiological intakes of soyfoods yield plasma levels of free, unconjugated genistein in the low nanomolar range. These concentrations may be sufficient to achieve meaningful activation of ERbeta, while having minimal impact on ERalpha (hence explaining why high-soy diets don't have feminizing effects, known to be mediated by ERalpha).[296] In contrast to ERalpha, ERbeta tends to have anti-proliferative, pro-apoptotic, and differentiating effects on tissues which express it – and all the cancers for which soy is believed to be protective arise from tissues which express ERbeta.[297-299] In tissues which express both isoforms of the estrogen receptor, ERbeta appears to antagonize the cancer-promotional effects of ERalpha. This may rationalize the curious observation that, in East Asian studies, high soy intakes are associated with decreased risk for breast cancer and with improved prognosis in women who have breast cancer[285] – despite the evident promotional impact of high estrogen exposure on this cancer. Colon epithelium, not ordinarily thought of as an estrogen sensitive tissue, expresses solely ERbeta.[300] This may explain not only the favorable impact on colorectal cancer risk associated with dietary soy, but also the reduction in risk for this cancer seen in postmenopausal women who use estrogen replacement therapy.[301, 302] With respect to gastric cancer, gastric epithelium expresses both ER isoforms, loss of expression of ERbeta correlates with poor prognosis in gastric cancer, and this malignancy is only about half as common in women as in men.[303-305]

How ERbeta might influence cox-2 expression is not clear. Nonetheless, there are several reports that ingestion of soy isoflavones can suppress induction of cox-2. This has been observed in the colonic mucosa of rats treated with the carcinogen dimethylhydrazine, in the uteri of ovariectomized mice treated with estrogen, and in the prostate cancers of patients administered soy isoflavones for two weeks prior to prostatectomy.[306-308] Also pertinent is a report that an ERbeta-selective agonist can inhibit induction of cox-2 in keratinocytes exposed to UV light or TNFalpha[309] – in nice accord with evidence that oral or topical soy isoflavones can inhibit photoaging.[310, 311] Further studies should determine whether and how ERbeta activation can suppress cox-2 induction in various tissues which express this receptor. (Those examining the pertinent literature should be cautioned that most in vitro studies with genistein are physiologically irrelevant, owing to the fact that they employ supraphysiological micromolar concentrations that would be expected to activate both ER isoforms, and to exert additional effects such as tyrosine kinase inhibition; moreover, rodent studies involving high isoflavone intakes may be a poor guide to human experience, as these high intakes may activate ERalpha.[296])

As a proviso, there is evidence that, within the context of a vegan diet, high intakes of soy protein may boost IGF-I levels, probably reflecting the fact that soy protein is one of the higher quality plant proteins.[224, 312] So vegans wishing to achieve a high intake of soy isoflavones might be well advised to ingest an isoflavone supplement rather than ingesting very large amounts of soyfoods or soy protein.

A Lifestyle Protocol for Minimizing Cancer Risk

The key point of this essay is that scope for human cancer prevention may be huge. The results of the recent aspirin meta-analyses – suggesting a reduction of cancer mortality by about one-third in subjects taking aspirin for at least 7.5 years – can justly be called astounding. Yet the protection from "Western" cancers enjoyed by Japanese in 1955 – most of whom were not taking aspirin! – is even more dramatic. There is good reason to suspect that an optimally-designed cancer-preventive lifestyle, integrating a range of protective options that target cox-2 bioactivity (albeit exerting a number of complementary cancer-preventive effects), could have a huge impact on cancer risk – a benefit that is all the more valuable given the likelihood that a "magic bullet" for cancer therapy seems likely to elude us for quite some time, if not permanently.

In light of the above discussion, such a lifestyle could include:

A whole-food plant-based diet (no or minimal animal protein), low in saturated and omega-6 fats, moderate in monounsaturates (as from almonds and olive oil) and in protein, and rich in fruits, vegetables and herbs that provide phase 2 inducers (crucifera, garlic and onions, green tea, etc.) and vitamin C;

Aerobic exercise training configured in a way that promotes leanness and good insulin sensitivity;[313-315]

Daily low-dose aspirin, enteric-coated;

A supplementation regimen including vitamin D (4,000-10,000 IU daily), EPA/DHA (or stearidonic acid, when available), spirulina (or PhyCB-enriched spirulina extracts), astaxanthin, melatonin (before bedtime), nutraceutical phase 2 inducers (reasonable choices could include lipoic acid, green tea polyphenols, aged garlic extracts, sulforaphane), N-acetylcysteine, soy isoflavones, and vitamin B12;

And - for the truly dedicated - moderate calorie restriction achieved by strategies such as modified alternate day fasting or carbohydrate-concentrated dieting.

Finally – this should be too obvious to mention! – don't smoke or drink alcohol abusively. Folate supplementation may be advisable in those who drink moderately. Heavily salted foods should not be eaten regularly, and microbial contamination of food should be avoided by refrigeration and other appropriate measures.

Importantly, this strategy - especially if complemented by moderate salt restriction and high potassium intake - could also be expected to minimize risk for vascular disorders, type 2 diabetes, and dementia, and hence would be expected to have a remarkably favorable impact on healthful lifespan.

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