Inflammation and cancer: an epidemiological perspective

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Abstract. Many chronic inflammatory conditions increase the risk of cancer in affected tissues. Clinical conditions that involve both inflammation and increased cancer risk include a broad range of immunological disorders, infections (bacterial, helminthic, viral), and chronic chemical and mechanical irritation. For example, the inflammatory bowel diseases, ulcerative colitis and Crohn’s disease, predispose to the development of cancers of the large bowel and/or terminal ileum; chronic infection with the bacterium Helicobacter pylori causes atrophic gastritis, dysplasia, adenocarcinoma and an unusual form of gastric lymphoma; and parasitic infection with schistosomes and other trematodes cause cancers of the urinary bladder and the intrahepatic and extrahepatic biliary tract. Chronic reflux of gastric acid and bile into the distal oesophagus causes chemical injury, Barrett’s oesophagus and oesophageal adenocarcinoma. Chronic cholecystitis and gallstones predispose to cancer of the gallbladder. Besides these clinical syndromes, subclinical inflammation may promote the development of certain tumours. The expression of COX-2 and lipid mediators of inflammation increases during the multistage progression of these tumours. Non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit COX-2 activity and tumour development in many experimental and clinical settings, are inversely associated with certain cancers in epidemiological studies. Despite their promise, however, anti-inflammatory drugs are not yet recommended for the prevention or treatment of any cancers. Numerous questions must be resolved concerning their molecular and cellular targets of action, efficacy, safety, treatment regimen, indications, and the balance of risks and benefits from treatment in designated patient populations.


The hypothesis that chronic irritation or injury may predispose to the development of certain cancers was raised by Virchow in the mid-19th century (Parsonnet 1999). He theorized that chronic irritation may establish the setting in which cells grow abnormally, as exemplified by bladder cancer occurring in patients from North Africa infected with Schistosoma haematobium (Parsonnet 1999). Numerous case reports and clinical series have described carcinomas of the skin arising as a complication of burns and scars, chronic sinus tracts, fistulas (Kaplan 1987,
Scotto et al 1996) and ulcers (Parsonnet 1999). Lung carcinomas have been reported at the site of scar tissue in patients with previous tuberculosis (Auerbach et al 1979) and sarcomas can occur as a complication of surgical implants and foreign bodies (IARC 1999). However, the evidence implicating many of these chronic inflammatory conditions with cancer is limited. Much of the information derives from case reports. Scar tissue that adjoins a carcinoma may be a consequence rather than a cause of tumour growth (Blot & Fraumeni 1996). In any event, the great majority of cancers that occur arise in patients and tissues with no obvious chronic inflammatory disease.

A more contemporary version of Virchow’s hypothesis is that the inflammatory processes induced by chronic injury contribute to the multistage development of cancer and that these, rather than the specific cause of the injury, account for the carcinogenicity in the majority of settings listed above. Inflammation involves a complex of host responses that, in the context of acute injury, promote wound healing and tissue regeneration. These responses include recruitment of specific types of cells, release of inflammatory mediators and interactions among chemokine ligand/receptor systems. Leukocytes (neutrophils, monocytes, macrophages, and eosinophils) generate reactive oxygen and nitrogen species that can directly damage the genes that control cell growth (Christen et al 1999). Cells that mediate the inflammatory response release autocrine and paracrine factors that stimulate cell proliferation, inhibit apoptosis, induce angiogenesis, and impair certain immune responses. Collectively, these factors can accelerate mutagenesis, promote the survival and clonal proliferation of mutated cells, and increase the probability that a particular clone of cells will acquire the requisite genetic mutations to become an invasive and metastatic cancer.

Even in the absence of overt inflammation, many of the same factors that mediate the acute inflammatory response are also produced by solid tumours at various stages of their development. For example, factors that stimulate cell proliferation, inhibit apoptosis and induce angiogenesis are involved in both wound healing and carcinogenesis. Enzymes like the inducible form of cyclooxygenase (COX-2) are expressed during wound healing and certain stages of neoplasia and increase production of inflammatory mediators. Much of the ongoing research on inflammation and cancer now focuses on the potential role of subclinical inflammatory mediators on the development of a wide range of cancers rather than on clinical inflammatory conditions known to predispose to specific cancers.

This overview considers three lines of evidence that are relevant to the hypothesis that chronic inflammation promotes the development of certain cancers. First it describes the broad spectrum of clinical disorders that involve both chronic inflammation and increased cancer risk. These include chronic inflammation from certain immunological conditions (ulcerative colitis, Crohn’s
disease, etc.), from chemical or mechanical irritation (reflux oesophagitis, gall stones), and from selected infections (bacterial, helminthic and viral) (Shacter & Weitzman 2002). Next it considers the increased expression of various inflammatory mediators that occurs during the development of various tumours. Finally, it considers the epidemiological, clinical and experimental evidence that non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the occurrence or progression of certain cancers (Thun et al 2002).

Clinical conditions that involve chronic inflammation and cancer

Clinicians have long been aware that a wide variety of chronic inflammatory disorders predispose to malignancy in the affected organ(s). Table 1, modified from Shacter & Weitzman (2002), lists examples of chronic inflammatory diseases that give rise to carcinomas and/or sarcomas. The only haematopoeitic cancer mentioned in Table 1 is the mucosa-associated lymphoid tumour (MALT), an unusual lymphoma that, like gastric adenocarcinoma, can be induced by chronic infection with Helicobacter pylori. Other conditions that predispose to lymphoma through chronic immune stimulation, and viral agents thought to induce cancer through direct interactions with host DNA, are not included in Table 1.

Idiopathic immunologically mediated conditions

Inflammatory bowel disease (IBD). Ulcerative colitis and Crohn’s disease are related but clinically and histologically distinct inflammatory diseases of the bowel that predispose to adenocarcinomas of the large bowel, terminal ileum, and in some cases extraintestinal sites including the biliary tract (Podolsky 2002). Tumours often occur at the site of chronic inflammation (Fenkel 2002). In ulcerative colitis the intestinal inflammation is limited to the colon and rectum, whereas in Crohn’s disease, two-thirds of patients have inflammation and increased risk of cancer in the terminal ileum. Inflammation is thought to result from a combination of genetic susceptibility and inappropriate activation of the mucosal immune system by normal luminal flora (Podolsky 2002). The absolute risk of developing colorectal cancer is high when extensive disease begins at a young age. Forty percent of patients diagnosed with pancolitis from ulcerative colitis before age 15 years developed colon cancer during 20-years of follow-up in a population-based linkage study in Sweden (Ekbom et al 1990). Numerous specific and non-specific inflammatory factors are expressed in patients with these conditions. These include phagocytic products (oxygen metabolites, nitric oxide, collagenases, etc.), toxic lymphocyte products, cytokines (including chemokines), neuropeptides and various components of plasma proteolytic cascades (Podolsky 2002).
Other immunological diseases. Various other idiopathic immunologically-mediated conditions that predispose to certain cancers are listed in Table 1. These include primary sclerosing cholangitis, lichen sclerosis, oral lichen planus and autoimmune gastritis. The list is not intended to be inclusive. Not mentioned are Hashimoto’s thyroiditis or Sjogren’s syndrome, which are associated with lymphomas but not solid cancers (Ron 1996). Lymphomas may arise from chronic polyclonal stimulation of immune cells leading to monoclonal proliferation rather than from more general inflammatory processes.
Chemical and mechanical irritation

Gastroesophageal reflux. Chronic reflux of gastric acid and bile from the stomach into the distal oesophagus causes chemical inflammation and histological abnormalities known as Barrett oesophagus (Shaheen & Ransohoff 2002). Damaged squamous cell epithelium of the lower oesophagus is replaced by metaplastic intestinal-type columnar epithelium that in some patients progresses to high-grade dysplasia. The risk of developing adenocarcinoma is estimated to be 0.5% per year among all patients with Barrett oesophagus, but 25% among those with high-grade dysplasia (Shaheen & Ransohoff 2002). Aggressive treatment with proton pump inhibitors has not been shown to induce regression of the histological abnormalities. The incidence of oesophageal adenocarcinoma has increased more rapidly than that of any other cancer in the USA since the mid-1970s (Devesa et al 1998).

Familial pancreatitis, sporadic chronic pancreatitis and haemachromatosis all cause chemically induced chronic inflammation with increased risk of cancer in the affected organ.

Gallstones. Chronic cholecystitis from recurrent or persistent gallstones predisposes to biliary tract cancer. The risk of gallbladder cancer is reportedly 4–5 times higher in patients with than without gallstones (Lowenfels et al 1999). Factors that predispose to gallstone formation are also risk factors for biliary tract cancer. These include obesity, multiple pregnancies and a genetic disorder of cholesterol metabolism prevalent among indigenous populations of North and South America.

Pneumoconioses. Asbestos fibres deposited in the lung and pleura cause chronic inflammation, asbestosis (pleural plaques and interstitial fibrosis), and increased risk of both mesothelioma and lung cancer (IARC 1977). Exposure to crystalline silica causes both pulmonary fibrosis and increased risk of lung cancer (IARC 1997).

Surgical implants. Metal nails and implants, as in hip replacement, are occasionally associated with cancers of the bone and other adjacent tissues at the site of the implant (IARC 1999). This literature consists largely of case-reports rather than systematic epidemiological studies.

Infectious conditions

Bacterial — Helicobacter pylori. Clinical, epidemiological, and experimental studies have established that the bacterium H. pylori is the principal cause of both gastric adenocarcinoma and of an uncommon mucosa-associated lymphoid tissue
(MALT) lymphoma of the stomach (IARC 1994a, Suerbaum & Michetti 2002). *H. pylori* is a Gram-negative, spiral bacteria that colonizes the mucus layer of the stomach. Its pathogenicity is greatest when colonization begins in childhood and involves more virulent strains that express the CagA (a 128 kDa cytotoxin-associated gene A-positive) protein. Adverse effects are also modified by host factors such as diet and genetic susceptibility (Yamaguchi & Kakizoe 2001). Persistent infection causes the development of chronic atrophic gastritis, achlorhydria, intestinal metaplasia, dysplasia and adenocarcinoma in susceptible persons. Similar findings are seen in experimental studies of ferrets and rhesus monkeys infected with other species of *Helicobacter* (Nightingale & Gruber 1994). Premalignant gastric lesions (Correa et al 2000) and low grade B cell gastric lymphomas (Wotherspoon et al 1993) may regress following successful eradication of the infection. Inflamed gastric epithelium is a rich source of interleukin 8 (IL8) and epithelial-cell-derived neutrophil-activating peptide 78 (Suerbaum & Michetti 2002). Cytotoxic strains of *H. pylori* that produce CagA+ induce greater production of IL8 from gastric epithelial cells.

**Bacterial other.** Other examples of chronic bacterial infection that may increase cancer risk include chronic osteomyelitis (predisposing to cancers of the skin and bone), chronic draining fistulas (causing local squamous cell carcinomas of the skin), chronic indwelling catheters (causing cystitis and bladder cancer) and cervicitis from *Chlamydia*.

**Helminth infections — Schistosoma haematobium.** Chronic infection with *Schistosoma haematobium* accounts for a substantial fraction of cancers of the urinary bladder in Egypt, where bladder cancer comprises approximately one-third of all cancers in men (Ferlay et al 2000). Many of the severe pathological manifestations of schistosomiasis such as ulcers, bladder polyps, fistulæ, and strictures result from the physical and immunological response of the host to the eggs rather than direct effects of the organism (Rosin & Hofsath 1999). The eggs from *S. haematobium* are deposited largely in the terminal ureters and bladder (IARC1994a). Egg deposition stimulates the activation and recruitment of monocytes and other leukocytes, which contribute to chronic ulceration. Egg remnants have been demonstrated in 82% of patients with urinary bladder cancer from *S. haematobium* in one large case series in Egypt (El-Biokany et al 1981). The bladder tumours associated with *S. haematobium* are typically squamous cell rather than transitional carcinomas. There is some evidence implicating another species of schistosome, *S. japonicum* in colorectal cancer (Rosin & Hofseth 1999), although the International Agency for Research on Cancer (IARC) has classified this evidence as ‘limited’ (IARC 1994a).
Infection with other trematodes. Three species of liver fluke infest the intrahepatic bile ducts of people who consume raw fish in parts of Southeast Asia (Opisthorchis viverrini), China and neighbouring countries (Clonorchis sinensis), and the former Soviet Union and Eastern Europe (O. felineus). These trematodes attach themselves to the intra- and extra-hepatic bile ducts where the adult parasite survives for 25–30 years (Thamavit et al 1999). All three species cause chronic inflammation and fibrosis, but only O. viverrini has been studied systematically and classified as a definite human carcinogen by IARC (IARC 1994a). Chronic inflammation is thought to cause progression from metaplasia, to dysplasia and cholangiocarcinoma.

Viral infections. Most hepatocellular carcinomas (HCC) in persons with chronic hepatitis B or C infection occur in conjunction with cirrhosis or chronic hepatitis (IARC 1994b). Recurrent cycles of inflammation, necrosis and regeneration appear more important to the carcinogenicity of HBV and HCV than are direct effects of the virus on host DNA (IARC 1994b). Infection acquired in early childhood confers the highest risk of cirrhosis and hepatocellular carcinoma. Prospective studies have shown that the incidence of HCC is more than 100-fold greater in patients with chronic HBV infection than in uninfected individuals (Robinson 1999).

Other viruses known to cause cancer include human papilloma virus (cervix, vulva, anus, penis, possibly oropharynx and oesophagus), Epstein Barr virus (lymphoma, nasopharynx), Kaposi’s sarcoma-associated herpes virus, and human T-cell leukaemia viruses (HTLVs). Although inflammation occurs at certain stages in the development of these tumours, it is difficult to separate the direct oncogenic effects of these viruses on DNA from their secondary effects on the immune system or from pathways involving chronic inflammation.

Insights regarding clinical inflammation and cancer

In summary, a broad range of human disorders cause chronic inflammation and predispose to increased risk of cancer in the affected organ(s). These provide strong observational support for the hypothesis that chronic inflammation contributes causally to the development of at least some of these tumours, but do not prove the hypothesis. Researchers have not yet identified specific therapeutic targets that inhibit tumour development in these settings. In some conditions, such as chronic viral infections, the inflammatory processes cannot be completely separated from the direct effects on DNA caused by the underlying pathogen. In others, such as inflammatory bowel disease, reflux oesophagitis and mechanical irritation from gallstones, the inflammatory response itself is clearly the principal determinant of cancer risk. These disorders, particularly the conditions that are not
amenable to antibiotic therapy, provide clinical opportunities to assess mechanism and to conduct randomized clinical trials.

Diseases that involve persistent clinical inflammation differ in severity from conditions in which inflammatory mediators may be expressed at subclinical levels in one or more stages of the development of certain cancers. However, the mechanisms by which chronic inflammation affects the development of human cancer may be the same. All of these conditions involve factors that may stimulate cell proliferation, suppress apoptosis, induce angiogenesis and disrupt other aspects of host immunity. These clinical settings provide opportunities to examine the role of specific cytokines in initiating or maintaining the inflammatory response and the role of reactive oxygen and nitrogen species in causing mutations. They also provide opportunities for randomized clinical trials to determine whether anti-inflammatory drugs prevent the occurrence or progression of neoplasia.

**Expression of inflammatory mediators during tumour development**

A second line of evidence concerns the increased expression of inflammatory mediators that occurs during tumour development. Numerous studies have shown that the inducible isoform of cyclooxygenase, COX-2, is over-expressed during the development of many cancers (reviewed in Gupta & DuBois 2001, Masferrer et al 2000). COX-2 is the inducible isoform of cyclooxygenase, the rate-limiting enzyme that converts arachidonic acid to prostaglandins and other metabolites. Increased expression of COX-2 has been documented in biopsies from colorectal adenomas and from carcinomas of the colon, stomach, oesophagus, pancreas, bladder, skin (non-melanoma), lung, head and neck and from melanoma (reviewed in Thun et al 2002, Masferrer et al 2000). The increased expression of COX-2 in many human tumours has stimulated numerous clinical and experimental studies that demonstrate that tumour growth can be inhibited by COX-2 inhibiting drugs and/or by genetic knockout of COX-2 activity (Thun et al 2002). Collectively, these studies provide strong evidence that lipid mediators of inflammation contribute to the multistage development of multiple cancers.

Although COX-2 is an attractive target in studies of chronic inflammation and cancer because of the availability of NSAIDs that selectively block COX-2 activity, many questions remain about the role of COX-2 in tumour development. Researchers have not yet identified the mechanism by which lipid mediators modulate apoptosis and angiogenesis in various experimental models, nor the relevance of these models for human cancers. Furthermore, the intensity of COX-2 expression varies widely across different types of tumours. It is not clear whether and in which clinical situations COX-2 actually contributes to tumour
progression or how the effects of COX-2 may vary depending upon the cellular
target.

There has been less research on the role of cytokines and other inflammatory
mediators in tumour development. Mantovani et al (2002) demonstrated that
serum levels of proinflammatory cytokines IL2, IL6, tumour necrosis factor
(TNF)α, leptin and C-reactive protein were higher in 82 advanced cancer patients
than in 36 controls. The concentration of C-reactive protein in plasma was reported
to correlate inversely with survival in cancer patients with multiple myeloma,
melanoma, lymphoma and tumours of the ovary, pancreas and gastrointestinal
tract (Mahmoud & Rivera 2002). Although cancer researchers have begun to
study cytokines as predictors of survival in patients with cancer, there have not yet
been studies that measure cytokine concentrations in serum or plasma before
the diagnosis of cancer as predictors of incidence. This is surprising,
since cardiovascular researchers have now established that circulating levels
of C-reactive protein, IL6 and other cytokines are strong and independent
predictors of coronary heart disease and stroke (Pradham et al 2002), and research
hypotheses regarding cardiovascular and cancer research are often pursued in parallel.

**Tumour inhibition by NSAIDs**

A third line of evidence that links chronic inflammation in the development of
certain cancers involves studies of tumour inhibition by NSAIDs. Randomized
clinical trials have established that two NSAIDs, the prodrug sulindac and the
selective COX-2 inhibitor celecoxib effectively inhibit the growth of
adenomatous polyps and cause regression of existing polyps in patients with the
hereditary condition familial adenomatous polyposis (FAP). NSAIDs have been
shown to inhibit tumour development, restore apoptosis, and to suppress
angiogenesis in a variety of *in vivo* and *in vitro* experimental models (Thun et al 2002).

Numerous epidemiological (non-randomized) studies have found lower
incidence of adenomatous polyps and lower incidence or death from colorectal
cancer in persons who regularly use aspirin and other NSAIDs compared with
non-users (Fig. 1), although one study has not (reviewed in Thun et al 2002). Prolonged use of aspirin or other NSAIDs is consistently associated with
a 30–50% reduction in incidence or death rates from colorectal cancer in all but one

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**FIG. 1.** Epidemiological studies of the association between non-steroidal anti-inflammatory
drug (NSAID) use and colorectal cancer or adenomatous polyps. The relative risk estimates
(circles) and 95% confidence intervals (lines) refer to the incidence or death rates among
regular NSAID users compared to that of non-users in (A) cohort studies and (B) case-
control studies of NSAIDs and colorectal cancer, and (C) studies of NSAIDs and
adenomatous polyps. Reproduced with permission from Thun et al (2002) which includes
details of references cited.
of these epidemiological studies (Fig. 1) (Thun et al 2002). Regular NSAID use is also associated with lower risk of cancer of the stomach (Fig. 2) and oesophagus (Fig. 3) in most studies (Thun et al 2002). NSAID use is associated with reduced risk of breast cancer in some studies (Fig. 4), but not in the Nurses’ Health Study (Egan et al 1996) nor in the large American Cancer Society Cancer Prevention Study (Thun et al 1993). Howe et al (2002) have proposed that NSAIDs may protect against breast cancer only in the subgroup of tumours that express HER-2/neu. Therefore, future studies should take into account the heterogeneity of tumour types.

Insights from research on NSAIDs and cancer inhibition

Collectively, the clinical, epidemiological and experimental studies provide strong evidence that arachidonic acid or its metabolites affect the development of certain cancers, particularly cancers of the colorectum, stomach, and oesophagus (reviewed in Thun et al 2002). Despite the strengths of these studies, however,
they do not provide randomized evidence that NSAIDs prevent the development of adenomatous polyps or cancer in the general population. Furthermore, studies have not yet defined the optimal drug, dose, treatment regimen, age to begin prophylactic therapy, or the balance of risks and benefits in different patient populations.

**Conclusions**

In summary, it is well established that a wide variety of chronic inflammatory diseases give rise to cancer, and that in some instances, the inflammatory response of the host rather than the specific cause of the injury appears to be the principal determinant of cancer risk. Besides these clinical syndromes, subclinical inflammation may promote the development of certain tumours. The concentration of COX-2 and related lipid mediators of inflammation increases during the multistage development of colorectal and other human cancers. It is biologically plausible that chronic inflammation predisposes to cancer, since cells involved in the immune response generate reactive oxygen and nitrogen species that are directly mutagenic, and release autocrine and paracrine factors that stimulate the clonal proliferation of genetically damaged cells. The resultant loss of tumour suppressor function, acquisition of oncogenes, and/or
FIG. 4. Epidemiological studies of the association between non-steroidal anti-inflammatory drug (NSAID) use and breast cancer. The relative risk estimates (circles) and 95% confidence intervals (lines) refer to the incidence or death rates among regular NSAID users compared to those of non-users.
loss of caretaker genes confers a selective growth advantage to mutated cells.

However, numerous questions must be answered before the current interest in inflammation and cancer can be translated into clinically useful therapies for the prevention or treatment of cancer. It has not yet been determined which aspects of the inflammatory process are critical to tumour development and which are incidental. Other questions concern the types of cancer and stages of development for which inflammation is important. Additional specific challenges are:

- to identify the molecular and cellular targets of anti-inflammatory drugs in cancer
- to determine the optimal drug, dose, and treatment regimen
- to assess the safety of treatment and the balance of risks and benefits in specific patient populations and
- to develop guidelines for clinicians and patients that take into account multiple health endpoints in patients with specific clinical profiles.

References


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**DISCUSSION**

*Harris:* Polymorphisms in any of these pathways could explain why some people are predisposed to cancer by inflammation and infection. Have you any idea what they are from these epidemiology studies?

*Thun:* At this point the epidemiological studies haven’t examined DNA markers of susceptibility to various inflammatory mediators in relation to cancer risk. This is possible because there are now very large prospective studies with thousands of cases, but it hasn’t yet been studied.

*Mantovani:* Are there polymorphisms for COX-2, and if so, have they been looked at in terms of susceptibility to neoplasia? This would be the logical connection.

*Ristimäki:* There are some polymorphisms in the COX-1 gene which may relate to thrombotic activity or to the response to aspirin, but I do not recall any functional polymorphisms in COX-2. When we consider the players of prostanoid biology we also need to consider enzymes upstream and downstream of COX-2 (PLA2 and the isomerase enzymes, respectively). Also, for every prostanoid there is a separate receptor. In cancer it looks like prostaglandin E2 is the key player, at least in gastrointestinal tract carcinomas. Thus, in addition to prostanoid-forming enzymes one might want to look for polymorphisms of the prostanoid receptor system (for further information see Papaftili et al 2002, Lin et al 2002, Humar et al 2000, Spirio et al 1998).

*Balkwill:* There have been several publications reporting associations with polymorphisms in inflammatory cytokine genes such as TNF and IL1, and cancer susceptibility and severity, although these have generally been in small numbers of patients (Warzocha et al 1998, Davies et al 2000, Oh et al 2000). In ovarian cancer we now have nearly 600 cases, and we find that a lot of these associations are lost when you look at larger numbers.

*Pepper:* There are also polymorphisms in VEGF, which is the major angiogenic factor. These are found both in the promoter and the 5′ UTR.

*Smyth:* In inflammatory bowel disease, cancer is quite rare. In those people with inflammatory bowel disease who actually get cancer, has anyone looked to see whether any of their inflammatory markers are different?

*Thun:* I don’t think that particular analysis has been done, but the analysis in Sweden showed that in people with pancolitis from an early age, the risk of developing cancer is actually quite high (40% over 20 year follow-up). The absolute risk depends mostly on the severity of the underlying disease and its duration. Most of the emphasis in ulcerative colitis has been looking at the genetic factors that predispose to this abnormal response to customary bowel flora, rather than being directed specifically at the inflammation.
Rollins: I want to amplify that question a little bit. In thinking about something like ulcerative colitis, it might be instructive to take the opposite view: perhaps the reason some of these patients develop colon cancer is because they have an underlying cancer susceptibility that is somehow related to the same susceptibility that puts them at risk for ulcerative colitis. Inflammation per se may just be an epiphenomenon. One of the reasons that I raise this issue is that when we look at the cumulative risk that Michael Thun showed, the patients who develop ulcerative colitis late in life, after age 40, have a more rapid rise in their risk of developing colon cancer. This suggests that inflammation per se may not be the causative agent. Perhaps we should be thinking a little sceptically.

Thun: That scepticism is a good thing to have, but let me put it in perspective. What is happening later in life is that the inflammatory process may be promoting an underlying phenomenon that is already more common. With other exposures that predispose to cancer, it is not uncommon that the absolute risk rises faster at older ages, because the exposure accelerates underlying processes that are already underway. Absolute risk is low at younger ages because you are starting de novo.

Oppenheim: There’s a general observation that the older you are the more cell-mediated (Th1-mediated) the inflammation becomes. Diseases such as mumps and chicken pox are perfect examples: people developing these diseases when they are older experience more of an inflammatory response. Perhaps the over-40 group also has more Th1 reactivity and therefore experiences more inflammation and more COX involvement. This may provide an explanation for this phenomenon of older subjects with colitis developing colon cancer more rapidly.

Harris: Some of the TNF blocking antibody and TNF soluble receptor studies in Crohn’s disease and ulcerative colitis imply that TNF could be a key player for these diseases, Crohn’s more clearly.

Mantovani: Are we eventually going to get useful information in this respect from patients who are being treated by anti-TNF and anti-IL1 for rheumatoid arthritis?

Feldmann: In the rheumatoid arthritis patients the only cancer risk that is increased is that of lymphomas. It is very striking that the local inflammatory site does not develop cancer, which is a big difference from the bowel. Crohn’s disease patients also have an increased lymphoma risk, so there is some common theme. Members of the TNF family are growth factors for precursor cells of lymphoma which form a type of lymphoma.

Balkwill: There is a big experiment going on with all the people who are having anti-TNF therapy, looking at cancer incidence in them. The only study I’m aware of involved following up about 700 patients for 3 years (Day 2002). The incidence of cancer in these people is about what you would expect.
Feldmann: Those studies are flawed by the problems of companies not really wanting to set up proper registers of all patients treated from the beginning. At the moment the consensus evaluation of the data is that there is no overall increased cancer risk, but the judgement is still out concerning lymphomas. Here the problem is that more severe rheumatoid arthritis gets more lymphoma and these are patients getting TNF inhibitors.

Gordon: Michael Thun, you talked about prospective trials, and case control and cohort studies. What would be the best way to look at this?

Thun: There are trials currently underway in patients with Barrett’s oesophagus, examining whether selective COX-2 inhibitors can induce regression of dysplasia. There has also been one small trial completed in Linxian, China, testing whether a selective COX-2 inhibitor could induce regression of precursor lesions for squamous cell oesophageal cancer. A high risk of squamous cell cancer of the oesophagus is endemic in this part of China because of nutritional deficiencies. That trial did not show any benefit from treatment with celecoxib with respect to regression of dysplasia. But it wasn’t a well-conducted trial. There is a larger trial underway in the USA testing whether celecoxib can induce regression of premalignant adenocarcinoma, and another trial assessing whether celecoxib is effective as adjuvant therapy in patients with Barrett’s oesophagus after ablation of the dysplasia. With respect to inflammatory bowel disease there was one epidemiological study from Sweden that showed that sulfasalazine, the salicylate that is given to treat inflammatory bowel disease was associated with lower risk of colorectal cancer. The problem in looking at people who are being given blockers of TNF receptor is that the number of subjects is not large enough to produce adequate results.

Feldmann: The numbers are there now, with over 200 000 on anti-TNF antibody and over 100 000 on TNF receptor Fc.

Rollins: Speaking of numbers, is there any opportunity to mine the data in the Nurses’ or Physicians’ Health Study looking at salicylate use and cancer incidence?

Thun: Those analyses are included in my paper. The whole problem is that these are observational studies so they don’t give randomised evidence of efficacy. The two critical areas in which we currently lack information are the need for randomised evidence of efficacy and for quantitative assessment of safety: what is the balance of the effects of these treatments across a variety of cancers and other endpoints? The large prospective studies can be informative about the second but not about the first.

Feldmann: One of the key things about cancer mutations is that these involve important signalling molecules such as Ras and p53. Is it known whether in the cancers driven by inflammation the incidence of these mutations is the same in the same site of cancer when inflammation is less obvious?
**Richmond:** Certainly for melanoma, where the early sunburn during childhood is related to later development of cancer, there is a strong correlation between Raf and Ras mutations, as well as p16 mutations in most of those melanoma patients. I don’t think the correct study has been done where they can go back and track those patients to examine the early changes prior to the development of the lesions. It would be lovely to have a study like this.

**Ristimäki:** Colon cancer that is associated with ulcerative colitis is a disease where there is a distinct pattern of genetic changes when you compare it to sporadic colorectal cancer or those appearing in FAP patients. One of these distinct gene alterations is involved with p16. So there are distinct patterns, at least in some adenocarcinomas that arise from inflammatory background when compared with sporadic cases.

**Gordon:** Let’s turn to the infections, which could be easier to analyse, such as *H. pylori* or hepatitis.

**Thun:** In the case of *H. pylori*, the recommended procedure is to treat the underlying infection. I don’t know the natural history of dysplasia in people after successful treatment of *H. pylori*. But characterizing this better would be very useful. In the case of hepatitis, I am not aware that NSAIDs have been used as part of adjuvant treatment. It is something to consider. The only question that will arise concerns whether there will be any adverse effects of giving COX-2 inhibitors to these patients.

**Gordon:** If we go beyond the COX-2 or arachidonate metabolites, and we don’t make any assumptions about the mediators, would this be a good group to utilize?

**Thun:** I think it is a really important group. Characterizing which inflammatory processes are most important might have huge clinical importance.

**Gordon:** What do you need? Is it the nature of the cells, or the subtleties of cellular responses, or different kinds of activation of macrophages? How far down can you usefully go?

**Thun:** This isn’t really my area; I’m not sure.

**Ristimäki:** In certain cases of gastric cancer it is very clear that the *H. pylori* infection has been gone for decades before cancer arises. Thus, the *H. pylori* may make the ground fruitful for carcinogenesis, but the actual cause of this (i.e. bacterial infection) has been long gone. It is the atrophic environment that is prone to genetic changes due to chemical insults. Thus, it may not be always the infection or inflammation itself but rather the histological changes caused by it that makes the individual more susceptible to the neoplastic transformation.

**Gordon:** One way round this, which we face with chronic diseases such as atherosclerosis, is to use transgenic mice in a controlled way to study spontaneous or chemical carcinogenesis, and then try looking at the inflammatory markers.
Strieter: Let me comment with regard to Th1/Th2 cells in the context of going back and using the tumour itself. The tumour and tumour microenvironment in general in terms of what we might perceive as an inflammatory response is more Th2-like, with a TGFβ predominance. This would allow one to potentially work backwards. The concept would be that if we end up with more of a Th2-like environment, this might be the sort of inflammation that ultimately leads to tumorigenesis and metastasis. In contrast, a Th1 response would eradicate whatever tumour associated antigen would be present and therefore would attenuate the evolution of tumorigenesis.

Harris: I am a little worried about simplistic approaches. Take angiogenesis. The vasculature in every tissue is different. We would expect the mechanisms of angiogenesis to be different in every sort of cancer, although there will be common themes. The same is likely to be true with inflammation. Although there may be some common players, each chronic disease has to be considered in its own right mechanistically.

Gordon: We have come a long way since Virchow in terms of being able to narrow down molecular targets.

Rollins: To go back to the question you posed earlier, I seem to remember that there have been studies giving COX-2 inhibitors to the Apc/Min mouse, and that they were effective. So people are beginning to do the kinds of things you are talking about.

Ristimäki: Not only that, but Professor Taketo’s group nicely showed that you can delete the Cox2 gene and see reduction in polyp size and number (allele dependently) in the Apc knockout mice (Oshima et al 1996). This genetic deletion is as effective as treating the Apc knockout mice with a COX-2 selective drug, suggesting that the drug is indeed attacking through COX-2 enzymes and not via some other targets.

Gordon: What we need is a mouse model that has a high expression of tumours, and then we cross it with a whole range of other knockouts.

Oppenheim: We can think of cancer as a two-signal event: both growth and mutation are needed. Inflammation is a process that stimulates growth and repair, and new cells are being brought in, so the opportunity for mutation is higher. In the models that people have been looking at, where does the gene defect come in? Does the inflammation per se also influence the gene defect, or is there some other signal that comes in?

Thun: In the case of the experimental studies related to COX-2, the Min mouse inherits one defective Apc allele, and has a high rate of losing function in the second allele. In colon cancer generally, the intrinsic processes provide an elevated mutation rate. Studies using the Min mouse model look at inhibition or acceleration of the process of tumorigenesis. Another whole line of experimentation in rats involves a chemical carcinogenesis. A known chemical
carcinogen is given to rats of various ages. Either at the beginning, after or prior to treatment, NSAID treatment is given, and the tumour occurrence is compared. Many studies of chemically induced colon cancer in rats show that NSAIDs inhibit the development of these cancers. Inhibition can be achieved at a lower dose if NSAID treatment is given before or at the beginning of carcinogen administration. With respect to colon cancer, the commonly used models involve both exogenous initiating agents and endogenous initiation.

Pollard: One of the questions about those sorts of experiments is whether they have been done with genetically disparate mice, where the bone marrow is genetically different from the rest of the animal, for example. This would tell us whether the COX-2 is in immune cells or within some other cell type. Has this been done yet?

Thun: With respect to the knockout mice, where all cells are affected, there is an interesting observation. The Cox2 knockout mice develop a lower incidence of colorectal cancer, but so do Cox1 knockout mice. This was not predicted by the COX-2 hypothesis. This observation raises an interesting question as to the role of COX-1, the constitutive form of the enzyme. It is conceivable that COX-1 plays some as yet undefined role in the induction of COX-2. As far as the attempt to figure out in which cells COX-2 is active, I am not aware of studies that have tried to examine this using knockouts in particular tissues. It has been more commonly studied by staining and using biopsy specimens, characterizing where the activity is.

Pollard: It seems to me to be crucial to use, for example a Cre-Lox system or bone marrow transplantation, so that COX-2 isn’t in the macrophages.

Gordon: Would you irradiate the animal before the adoptive transfer?

Pollard: It would need a control with normal bone marrow.

Ristimäki: There is one study in which Lewis lung carcinoma cells were injected into COX-2 knockout animals (Williams et al 2000). In this model less angiogenesis and tumour growth was seen in the COX-2 knockout mice than in the wild-type background. This suggests that the stromal cell COX-2 contributes to the behaviour of the tumour cells. Of course, this doesn’t dissect out which stromal cells are involved (i.e. vascular endothelial cells, macrophages or fibroblasts).

Pollard: It seems to me that in the context of inflammation and cancer, this is a critical experiment to do.

Ristimäki: It is critical also in the sense that in mice, COX-2 expression is almost exclusively found in the stroma, and not in the epithelial compartment as it is in human tumours. This is a difference between mice and men. Another difference is that all these FAP rodent models are not actually cancer models. They are pre-invasive lesions (adenomas), since the mice die before invasive cancers develop (due to gastrointestinal tract obstruction or bleeding). In humans we want to treat the invasive cancer and not let it metastasize.
**Forni:** Are there any examples of chronic inflammation that are not linked to an increase of cancer? What about tuberculosis? Is this considered to be a chronic inflammation?

**Gordon:** The textbooks say chronic inflammations such as tuberculosis are not linked to an increase of cancer, others such as *Schistosomiasis* may be.

**Oppenheim:** Psoriasis could be an example. It is chronic, inflammatory and long-lasting. I’m not aware that this has been associated with cancer.

**Mantovani:** It is a strictly Th1 disease.

**Ristimäki:** What about the other side of the coin? We have organ transplant patients who are treated with immunosuppressive drugs. Do they show a higher prevalence of certain types of cancers?

**Gordon:** Bob Schreiber has re-investigated the immune surveillance hypothesis in immunodeficient mice and now has evidence that the immune system does play a role in a range of tumour types.

**References**

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