

REVIEW ARTICLE

Cancer: A Mortal Disease And Improvement In The Technologies of Treatments

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ABSTRACT

Cancer is second only to heart disease as the leading cause of death in the world. Although surgical resection is considered to be the only approach that offers a possibility of cure to patients with cancer, the prognosis of the disease has not been improved markedly by any surgical procedures in the past 20 years. Although preoperative chemo radiation has various advantages in the treatment of cancer, it does not contribute to its down staging and eventual cure. Our review underscores the complexity of pathogenic mechanisms mediated by chronic inflammation, and identification of enzymes as a target to cure the cancer. The name of cancer is derived from the type of tissue in which it develops. Most human cancers are carcinomas, malignant tumors that arise from epithelial cells. Melanomas are cancerous growths of melanocytes, skin epithelial cells that produce the pigment melanin. Sarcoma a cancer arising from muscle cells or connective tissues. Leukemia is a cancer of blood forming organs characterized by rapid growth of abnormal leukocytes.

Key Words: Melanomas, Leukemia, Sarcoma, abnormal leukocytes.

INTRODUCTION

Cancer is a group of diseases characterized by uncontrolled or abnormal cell proliferation. When cells in a part of the body divide without control, the excess tissue that develops is called a tumor or neoplasma. The study of tumors is called oncology. Tumors may be cancerous and often fatal, or they may be harmless. A cancerous neoplasm is called a malignant tumor or malignancy. One property of most malignant tumors is their ability to undergo metastasis, the spread of cancerous cells to other parts of the body. A benign tumor is a neoplasm that does not metastasize. An example is a wart. Most benign removed surgically if they interfere with normal body function or become disfiguring. Some benign tumors can be inoperable and perhaps fatal.

Several factors may trigger a normal cell to lose control and become cancerous. Environmental agents: substance in air we breathe, the water we drink, and the food we eat. A chemical agent or radiation that produces cancer is called a carcinogen. Carcinogens induce mutations, permanent changes in the DNA base sequence of a gene. The world health organization estimates that carcinogens are associated with 60-90% of all

human cancers. Examples of carcinogens are hydrocarbons found in cigarette tar, radon gas from the earth, and ultra violet in sun light. Intensive research efforts are now directed toward studying cancer causing genes, or oncogenes. When inappropriately activated, these genes have the ability to transform normal cell into a cancerous cell.

Cancer Incidence Patterns in Different Regions of the Country:

Lung, oesophagus, stomach, oral and pharyngeal cancers are much higher in men while in females the cancers of cervix and breast are predominant forms followed by those of stomach and oesophagus. There is variation in the site wise distribution within the various population registries. Oesophageal cancers are often found in the southern states of India such as in Bangalore and Chennai and also in Mumbai and Ahmadabad. Stomach cancers are more common in southern India with the highest incidence in Chennai. Cancers of the oral cavity are high in Kerala (south India) and pharyngeal cancers in Mumbai (western India). Thyroid cancers among women are more common in Kerala. Gall bladder

cancerous high in northern India, particularly in Delhi and kolkata (Fig 1) [1-3].

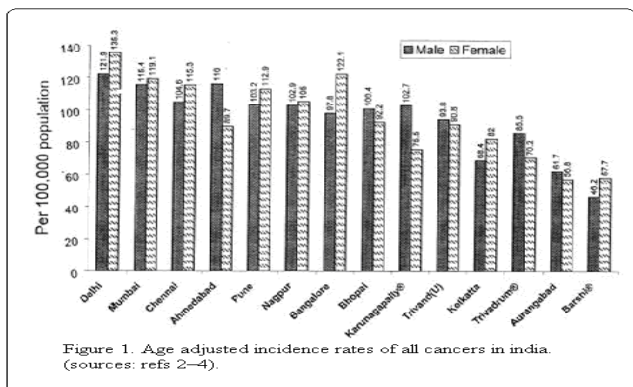


Fig 1

to be considered, as well as strengthening the epidemiological research capabilities of institutions in developing countries [4].

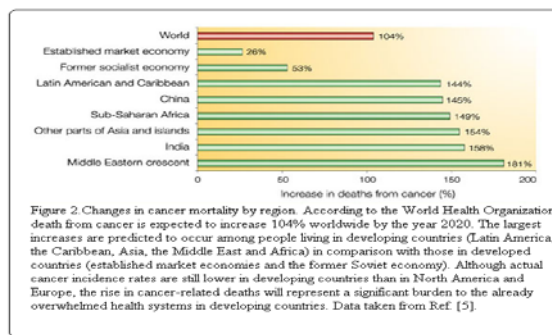


Fig 2

CYCLIN DEPENDANT KINASE
The Control of Cell Cycle

The incidence of cancer and other chronic diseases is increasing in developing countries owing to increased life expectancy and changes in risk factors that are concomitant with economic development. The dramatic improvements in life expectancy that are observed in middle-income countries can be attributed to better public health practices such as immunization and improved nutrition. This has reduced infant and child mortalities from infectious diseases and malnutrition. By contrast, according to the world health organization, mortality from cancer is expected to increase considerably in developing countries including Asia, Africa and Latin America (Fig 2). Although cancer incidence rates are still substantially lower in developing countries than in developed countries, the burden of cancer and other chronic diseases pose an important threat to already overwhelmed health-care systems. Changes in lifestyle and diet that occur with economic development typically include unhealthy practices such as sedentary behavior, smoking, increased total energy intake and consumption of highly refined foods, sugars, saturated fat and meats. These adaptations are due, in part, to the mechanization and modernization of processes ranging from transportation to household chores. Additionally there is increasing availability and demand for cheaper food options, which tend to be high in both fat and sodium and low in fiber. Such adaptations are often referred to as 'westernization' -- the umbrella term that encompasses these behaviors, which are common in North America and parts of Europe. Furthermore, key infrastructure requirements need

TUMOR NECROSIS FACTOR –A (TNF-A)

Tumor Necrosis Factor –α, Inflammation and cancer:

TNF- α was first isolated as an anticancer cytokine. Experience since then has indicated that when expressed locally by the cells of the immune system, TNF – α has a therapeutic role. However, when deregulated and secreted in the circulation, TNF - α can mediate a wide variety of disease, including cancer. TNF- α has itself been shown to be one of the major mediators of inflammation. Induced by a wide range of pathogenic stimuli, TNF- α induced other inflammatory mediators and proteases that orchestrate inflammatory responses. TNF - α is also produced by tumors and can act as an endogenous tumor promoter.

The role of TNF- α has been linked to all steps involved in tumor genesis, including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and the role of both TNF- α and its receptors has been examined in cancer development. Various approaches, including genetic deletion, transgenic models, and the use of antibodies and soluble receptors as decoys, have been used to gain insight into the role of TNF in tumor development. TNF receptor mediated signaling is required of skin cancer development induced by NF-kB signaling in driving skin cancer development [5].

In this commentary, we describe a model to explain the mechanism of the embryopathy of thalidomide. We propose that thalidomide affects the following pathway during development: insulin-like growth factor I (IGF-I) and fibroblast growth factor 2 (FGF-2) stimulation of the transcription of β3 integrin subunit genes. The resulting β3 integrin dimer stimulates angiogenesis in the developing limb bud, which promotes outgrowth of the bud. The promoters of the IGF-I and FGF-2 genes, the genes for their

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binding proteins and receptors, as well as the α and β 3 genes, lack typical tata boxes, but instead contain multiple GC boxes (gggccc). Thalidomide, or a breakdown product of thalidomide, specifically binds to these GC promoter sites, decreasing transcription efficiency of the associated genes. A cumulative decrease interferes with normal angiogenesis, which results in truncation of the limb. Intercalation into g-rich promoter regions of DNA may explain why certain thalidomide analogs are not teratogenic while retaining their anti-tumor necrosis factor- α (TNF- α) activity, and suggests that we look elsewhere to explain the action of thalidomide on TNF- α . On the other hand, the anti-cancer action of thalidomide may be based on its antiangiogenic action, resulting from specific DNA intercalation. The tissue specificity of thalidomide and its effect against only certain neoplasias may be explained by the fact that various developing tissues and neoplasias depend on different angiogenesis or vasculogenesis pathways, only some of which are thalidomide-sensitive^[6].

How thalidomide works in the treatment of cancer is not fully understood. Cancers need to produce a network of new blood vessels in order to grow. Without forming these new blood vessels, cancers cannot grow larger than a pinhead. Researchers hope that thalidomide can stop cancers from developing new blood vessels. This should reduce the cancer's supply of oxygen and nutrients, which, it is hoped, will cause the tumour to shrink, or at least to stop growing. Drugs that interfere with blood vessel growth in this way are called angiogenesis inhibitors or antiangiogenics^[7].

Thalidomide can also be helpful in reducing some of the unpleasant symptoms that people with cancer may have. A substance produced naturally in the body, called tumour necrosis factor (TNF), stimulates the immune system to attack any cells that may be harmful. When people have cancer, they may produce too much TNF. This causes their immune system to overreact and can lead to high temperatures, night sweats and severe weight loss. Thalidomide reduces the amount of TNF produced in the body and therefore may reduce these symptoms^[8].

Immunomodulatory drugs (IMiDs): The potent inhibition of TNF- α using IMiDs was first demonstrated in lps-induced pbmcs both *in vitro* and *in vivo*^[9-10]. It has been shown that relative to the parent drug thalidomide, the analogues

inhibited TNF- α more potently, as well as inhibiting lps-induced monocyte IL-1 β and IL-12 production, and enhanced the production of interleukin 10 (IL-10). The IMiDs had only partial inhibitory effect on IL-6. When tested *in vivo*, the amide analogues protected 80% of lps-treated mice against death from endotoxin-induced shock^[11]. Among the earliest studies done on IMiDs had been on multiple myeloma (mm) cell lines. This provided a pathobiologic rationale for the use of IMiDs since TNF- α is present locally in the bone marrow microenvironment and induces NF- κ B dependent up-regulation of adhesion molecules on both multi myeloma cells and bone marrow stromal cells, resulting in increased adhesion^[12]. This represents an attractive target for IMiDs in this disease entity. Although TNF- α has been shown to only modestly trigger the actual proliferation of multi myeloma cells, the subsequent activation of NF- κ B, a transcription factor that confers significant survival potential in a variety of tumors, also stimulate IL-6, another important survival signal, in bone marrow stromal cells^[13], both of which are potential targets of the IMiDs.

CYCLOOXYGENASE (COX): Cancer is the most common malignancy in women in industrialised nations and the second leading cause of female cancer-related mortality. Approximately 40 000 women develop breast cancer in the UK each year. The incidence of breast cancer has increased by two-thirds over the last 15 years. Mortality rates though have fallen by one-third, and this is likely to be due to earlier detection of breast cancer because of screening, and the increased use of adjuvant therapies. In recent times, the prospect of further improvements in mortality rates has grown with hope provided by new chemotherapy agents and monoclonal antibody therapy directed at cell surface molecules. But can we do even better for women with breast cancer using cheap and simple treatments that are in current use.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of widely available, inexpensive medicines. The analgesic, anti-inflammatory, antipyretic and antithrombotic effects of salicylate in willow bark and other plant extracts were recognised in ancient Egypt and Greece. These properties have been extensively exploited in numerous fields of clinical medicine since the 19th century, and in cancer patients primarily for analgesia.

NSAIDs inhibit the enzyme Cyclooxygenase (COX), which catalyses the conversion of arachidonic acid to prostaglandins (PGs). Prostaglandins are important mediators of signal transduction pathways and are involved in cellular adhesion, growth and differentiation. In recent years, interest has been aroused in a possible role for aspirin and other NSAIDs in the prevention of malignancy. The most persuasive evidence to date relates to colorectal cancer. Meta-analyses of observational studies suggest that NSAIDs reduce the risk of colorectal cancer by around a half^[14]. For this reason, the US food and drug administration (USFDA) has approved the use of the selective COX-2 inhibitor, celecoxib, in the prevention of colorectal polyps in patients with familial adenomatous polyposis. It has been suggested that there is a possible role for COX inhibitors in the chemoprevention, and possibly even treatment of breast cancer. In this article we review the current experimental, epidemiological and clinical evidence available on the possible link between COX and breast cancer, coming to a consensus as to whether COX inhibition is a worthwhile potential strategy in the prevention and treatment of breast cancer.

The Biochemistry of COX: NSAIDs inhibit the COX 1 and 2 enzymes, the rate-limiting enzymes in the conversion of arachidonic acid to prostaglandins. The two COX isoforms have distinct tissue distributions and physiological functions. Cyclo-oxygenase-1 is constitutively expressed in many tissues and cell types, whereas the inducible isoenzyme COX-2 is pro-inflammatory in nature and expressed only in response to certain stimuli such as mitogens, cytokines, growth factors, or hormones. Specific COX-2 inhibitors have been developed, and these largely avoid the gastrointestinal side effects associated with NSAID use, which are thought to be due mainly to COX-1 inhibition. Prostaglandins are important mediators of signal transduction pathways and are therefore involved in cellular adhesion, growth and differentiation.

COX, Prostaglandins and Cancer: There is a clear relationship between tissue prostaglandin levels in human breast tumours, the development of metastases and survival^[15-16]. The main product of COX-2, prostaglandin E₂, is synthesized by several human breast cancer cell lines and is found at high levels in tumour cells. High concentrations of prostaglandin E₂ have been associated with risk of metastases and a lack of oestrogen and progesterone receptors^[17].

COX-2 is over expressed in breast cancer cell lines such as the highly invasive, metastatic line MDA-MB-231 as well as in tumours. In one study, COX-2 expression was detected by PCR in 13 human breast tumours with no detectable expression in normal breast tissue. A correlation was also observed between COX-2 expression and increasing tumour cell density. Contrasting findings come from a series of 44 cases where COX-2 protein was detected in just two patients. Conclusions become clearer when larger numbers of patients' tumours are examined. In an immunohistochemical study of 1576 invasive breast carcinomas, there was moderate to strong COX-2 expression in 37% of the samples^[18-22]. This observation, which has been replicated in other studies involving large patient numbers, should be regarded as definitive, and the evidence from past studies should be disregarded because of the small sample size. COX staining is not specific to malignant cells but also detectable in premalignant breast tissue. A higher frequency of COX-2 was expressed in ductal carcinoma *in situ* than invasive breast cancer, suggesting that COX-2 may have a role in preinvasive disease. However, all is not as straightforward as it might first appear. It was found that there was no significant difference in COX-2 expression, comparing normal breast tissue from reduction mammoplasty and normal breast tissue surrounding ductal carcinoma *in situ*, and also no difference in COX-2 expression between ductal carcinoma *in situ* and invasive cancer.

COX-2 and Cancer Progression: COX-2 expression is correlated with prognostic markers that reflect a poor chance for survival, which includes tumour size, axillary node metastases, tumour grade, ductal histology, receptor negative disease and her-2 amplification moreover; elevated COX-2 expression has recently been shown to correlate with distant metastases in breast cancer^[23-25].

COX-2 is related to cancer outlook through direct and indirect mechanisms. Prostaglandins may directly stimulate mitogenesis through a direct effect on fibroblasts, osteoblasts, and mammary cells. COX-2 indirectly affects mutagenesis, angiogenesis, and increased cell migration and apoptosis. Celecoxib has been shown to inhibit proliferation of human breast cancer cell lines^[24].

The combination of COX-2 inhibitor with standard cancer chemotherapeutic and/or radiation may provide additional therapeutic paradigms in

the treatment of various human cancers.

Cyclooxygenase enzyme inhibitors:

Translational experiments in animal models link *cox* with breast cancer. Transgenic mice with the COX-2 gene inserted under the control of the mouse mammary tumour virus promoter developed mammary tumours after several cycles of pregnancy and lactation while virgin animals remain tumour free. This provides evidence that overexpression of COX-2 itself is sufficient to induce tumorigenesis, but of potentially greater clinical significance is the evidence that if the transgenics were given a COX-2 inhibitor, mammary tumorigenesis was repressed.

In another study using nonselective *cox* inhibitors, a 35-day course of ibuprofen administered to rats with carcinogen-induced mammary tumours, led to a significant reduction in tumour volume. The tumors showed reduced expression of both *cox* isoforms [25].

Specific COX-2 inhibitors can prevent mammary tumours from developing in experimental animals. Nimesulide reduced the size and numbers of carcinogen-induced tumours and celecoxib inhibited the development of carcinogen-induced mammary tumours. Celecoxib has also been shown to significantly delay the onset of *her2/neu*-induced tumours. *Her2/neu*-induced mammary tumours and angiogenesis have been shown to be reduced in COX-2 knockout mice [22, 25–26].

It has been demonstrated that PGE2 stimulates aromatase transcription leading to increased concentrations of estrogens. Over expression of *cox-2* in breast cancer may lead to increased PGE2 synthesis and this in turn to progression of oestrogen-dependent disease. Therefore, inhibition of PGE2 by COX-2 inhibitors may inhibit aromatase activity and when combined with aromatase inhibitors reduce tumours by inhibiting a common target. Indeed, there is preclinical data from a rodent model to suggest that celecoxib when combined with exemestane significantly inhibits the growth of mammary tumours [23, 24].

The antitumorigenic effects of NSAIDs and selective *cox-2* inhibitors may involve other mechanisms than COX-2 inhibition: for example, high concentrations of NSAIDs or selective inhibitors of COX-2 suppress the growth of cells in culture that do not express COX-2. Moreover, a recent clinical trial found that low-dose aspirin, which has virtually no COX-2 inhibitory effects, had a chemoprotective effect in individuals at

increased risk of developing colorectal cancer [27-28].

CONCLUSION

Most of the research into cancer has been done on people living in North America and Europe, representing only a fraction of the global population and their dietary patterns and lifestyle factors. The wide variety of diet, lifestyle and environmental exposures, as well as genetic variation between populations in developing countries, can add valuable information to our knowledge of the factors that contribute to the development of cancer. The international portfolio of cancer studies therefore needs to be expanded to developing countries. These types of studies would not only serve the needs of people in developing countries, but also progress our overall knowledge of cancer etiology. There are, however, many logistical issues that need to be addressed when performing epidemiological studies in developing nations. These include defining research priorities by taking into consideration past scientific discoveries so that efforts are not unnecessarily repeated and limited resources are preserved.

REFERENCES

1. Cancer Registry Abstract, Newslett. Natl. Cancer Registry Project India, 2001; 8: 1-5.
2. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J. Cancer Incidence in five continents. IARC Scientific Publications, Lyon. 1997; 1: 430.
3. Population based Cancer Registry Report 1991–95; Regional Cancer Centre, Trivandrum, 1999.
4. Murray, C. J. L., Lopez, A. D. & World Health Organization. The Global Burden of Disease, Volume 1. A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020 (Harvard University Press, Cambridge, Massachusetts, 1996).
5. Mitsiades N, Mitsiades CS, Poulaki V, et al. Biologic sequelae of nuclear factor-kappaB blockade in multiple myeloma: therapeutic applications. *Blood*. 2002; 99:4079–86.
6. Anderson KC, Jones RM, Morimoto C, Leavitt P, Barut BA. Response patterns of purified myeloma cells to hematopoietic growth factors. *Blood*. 1989; 73:1915–24.
7. Garcia Rodriguez LA, Huerta-Alvarez C. Reduced incidence of colorectal adenoma among long-term users of nonsteroidal anti-

- inflammatory drugs: a pooled analysis of published studies and a new population-based study. *Epidemiology*. 2000; 11: 376–381.
8. Bennett A the production of prostanoids in human cancers, and their implications for tumor progression. *Prog Lipid Res* 1986; 25: 539–542.
 9. Srey MP, Patel KV Prostaglandin E2 production and metabolism in human breast cancer cells and breast fibroblasts. Regulation by inflammatory mediators. *Br J Cancer* 1995; 72: 1412–1419.
 10. Fulton AM, Heppner GH Relationships of prostaglandin E and natural killer sensitivity to metastatic potential in murine mammary adenocarcinomas. *Cancer Res* 1985; 45: 4779–4784.
 11. Liu XH, Rose DP Differential expression and regulation of cyclooxygenase-1 and -2 in the human breast cancer cell lines. *Cancer Res* 1996; 56: 5125–5127.
 12. Parrett ML, Harris RE, Joarder FS, Ross M, Clausen K, Robertson F Cyclooxygenase-2 gene expression in human breast cancer. *Int J Oncol* 1997; 10: 503–507.
 13. Hwang D, Scollard D. Expression of cyclooxygenase-1 and cyclooxygenase-2 in human breast cancer. *J Natl Cancer Inst* 1998; 90: 455–460.
 14. Ristimaki A, Sivula J, Haglund C, Joensuu H, Isola J. Prognostic significance of elevated cyclooxygenase-2 expression in breast cancer. *Cancer Res* 2002; 62: 632–635.
 15. Boland GP, Butt IS, Bundred NJ. COX-2 expression is associated with an aggressive phenotype in ductal carcinoma in situ. *Br J Cancer* 2004; 90: 423–429.
 16. Ranger GS, Thomas V, Jewell A, Mokbel K Elevated cyclooxygenase-2 expression correlates with distant metastases in breast cancer. *Anticancer Res* 2004; 24: 2349–2351.
 17. Arun B, Zhang H, Mirza NQ Growth inhibition of breast cancer cells by celecoxib. *Breast Cancer Res Treat* 2001; 69: 234.
 18. Liu CH, Chang SH. Overexpression of cyclooxygenase-2 is sufficient to induce tumorigenesis in transgenic mice. *J Biol Chem* 2001; 276: 18563–18569.
 19. Narko K, Zweifel B, Lane TF, Hla T. COX-2 inhibitors and genetic background reduce mammary tumorigenesis in cyclooxygenase-2 transgenic mice. *Prostaglandins Other Lipid Mediat* 2005; 76: 86–94.
 20. Robertson FM, Parrett ML, Joarder FS. Ibuprofen-induced inhibition of cyclooxygenase isoform gene expression and regression of rat mammary carcinomas. *Cancer Lett* 1998; 122: 165–175.
 21. Nakatsugi S, Ohta T, Kawamori T, Mutoh M, Tanigawa T, Watanabe K, Sugie S, Sugimura T, Wakabayashi K Chemoprevention by nimesulide, a selective cyclo-oxygenase-2 inhibitor of 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine (PhIP)-induced mammary gland carcinogenesis in rats. *Jpn J Cancer Res*. 2000; 91: 886–892.
 22. Abou-Issa HM, Alshafie GA, Seibert K, Koki AT, Masferrer JL, and Harris RE Dose–response effects of the COX-2 inhibitor, celecoxib, on the chemoprevention of mammary carcinogenesis. *Anticancer Res* 2001; 21: 3425–3432
 23. Howe LR, Subbaramaiah K, Patel J, Masferrer JL, Deora A, Hudis C, Thaler HT, Muller WJ, Du B, Brown AM, Dannenberg AJ Celecoxib, a selective cyclooxygenase inhibitor, protects against human epidermal growth factor receptor 2 (HER-2)/neu-induced breast cancer. *Cancer Res* 2002; 62: 5405–5407.
 24. Howe LR, Chang SH, Brown AM, Hla T, Subbaramaiah K, Dannenberg AJ HER2/neu-induced tumorigenesis and angiogenesis are reduced in cyclooxygenase knockout mice. *Cancer Res* 2005; 65: 10113–10119.
 25. Harris RE, Robertson FM, Abou-Issa JM, Farrar WB, Brueggemeier R Genetic induction and up-regulation of cyclooxygenase (COX) and aromatase (CYP 19): an extension of the dietary fat hypothesis in breast cancer. *Med Hypotheses* 1999; 52: 291–292.
 26. Pesenti E, Masferrer JL, di Salle E Effect of exemestane and celecoxib alone or in combination on DMBA-induced mammary carcinoma in rats. *Breast Cancer Res* 2001; 69: 288 (Abstract 445)
 27. Hwang DH, Fung V, Dannenberg AJ National Cancer Institute Workshop on chemopreventive properties of nonsteroidal anti-inflammatory drugs: role of COX-dependent and independent mechanisms. *Neoplasia* 2002; 4: 91–97
 28. Huls G, Koornstra JJ, Kleibeuker JH Nonsteroidal anti-inflammatory drugs and molecular carcinogenesis of colorectal carcinomas. *Lancet*. 2003; 362: 230–232