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Anti-Cancer Potential of Cyclooxygenase-2-Inhibitors

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Abstract: ***Cyclooxygenase-2-Inhibitor is mostly used in Non-Steroidal Anti-Inflammatory Drug [NSAID] They are the most often used class of medications, primarily in the treatment of degenerative joint illness, rheumatic diseases, metabolic disorders, cardiovascular disturbances, infections, and other pain and inflammation-related diseases. Although long-term NSAID use was found to be associated with a decreased risk of developing breast cancer in Women. The activity of COX-2-Inhibitor is confirmed with reduced Carcinogenesis. COX-2 inhibition appears to prevent the development of breast tumours in women with breast cancer. Nonselective inhibitors like indomethacin, flurbiprofen, and aspirin, for example, have been shown to lessen the frequency of carcinogen-induced tumors. Furthermore, COX-2 inhibitors that are preferred or selective, such as celecoxib and nimesulide, have been shown to delay carcinogenesis and reduce disease incidence.***

Keywords: Cyclooxygenase-2-Inhibitor, NSAID, Carcinogenesis, Breast cancer, Apoptosis, Celecoxib

1. Introduction

Cyclooxygenase-2-Inhibitor has multiple therapeutic effect in human bodyEpidemiologic and laboratory investigations suggest that Non-steroidal anti-inflammatory drugs (NSAIDs) have chemo preventive effects against breast cancer due to their activity against cyclooxygenase-2 (COX-2), the rate-limiting enzyme of the prostaglandin cascade. Selective COX-2 inhibitors (celecoxib and rofecoxib) were only recently approved for use in 1999, and rofecoxib (Vioxx) was withdrawn from the marketplace in 2004 (Regulski et al., 2016). Nevertheless, even in the short window of exposure to these compounds, the selective COX-2 inhibitors produced a significant (71%) reduction in the risk of breast cancer, underscoring their strong potential for breast cancer chemoprevention. Bone is the predominant site of metastasis in case of breast cancer. Breast cancer cells isolated and cultured from the bone metastases produced significantly more prostaglandin E2 (an important mediator of COX-2) than the parental injected cell populations of breast cancer cells. Next, COX-2 inhibitor, MF-tricyclic, inhibited bone metastasis caused by a bone seeking clone both in prevention regimen. These studies indicate that COX-2 produced in breast cancer cells may be vital to the development of osteolytic bone metastases in patients with breast cancer, and that COX-2 inhibitors may be useful in halting this process.

Breast cancer accounts for 23% of female cancers and is the most frequent cause of cancer-related death among women worldwide. Aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and selective COX-2 inhibitors, hereafter referred to as COX-2 inhibitors, are effective analgesic, anti-pyretic, and anti-inflammatory drugs. They exert pleiotropic effects, including the prevention of cardiovascular disease and cancer, although the latter may be confined to subpopulations. Aspirin, NSAIDs, and COX-2 inhibitors target the cyclooxygenase enzymes, COX-1 and COX-2. These enzymes promote angiogenesis and prevent apoptois (Harris et al., 2006). COX-1 is ubiquitously expressed, but COX-2 is expressed only during inflammation and in cancer. Elevated COX-2 and its products, prostaglandins, correlate with shorter breast cancer survival. Cell line and animal model research suggests that NSAIDs, aspirin, and COX-2 inhibitors impede breast cancer cell growth.

Evolution of Breast Cancer:

The first major gene associated with hereditary breast cancer was BRCA1, located on chromosome 17. This gene was identified in 1990 using linkage analysis in families with suggestive pedigrees. In 1994, BRCA2 was mapped to chromosome 13. A mutation in either BRCA1 or BRCA2 confers an increased risk of breast and other cancers. Large rearrangements and deletions in BRCA1 or BRCA2 can also alter the function of BRCA, resulting in an identical clinical syndrome to that seen in carriers of mutations in these genes (Singh et al., 2007). The clinical syndrome seen in BRCA mutation carriers is referred to as the Hereditary Breast/Ovarian Cancer (HBOC) syndrome, though there are patients with this same clinical picture who are found to be negative for mutations in both BRCA1 and BRCA2. Research in HBOC has focused on determining the associated risk of breast and other cancers, identifying specific clinical and histopathological features, and developing therapeutic and prevention strategies. Tumors due to mutations in BRCA1 tend to be of the basal-like phenotype, have a high histologic grade, and do not commonly express the estrogen receptor (ER), progesterone receptor (PR), or Her2/neu, the so-called triple-negative tumor. BRCA2-related tumors more closely resemble sporadic tumors. BRCA1 and BRCA2 mutations are inherited in an autosomal dominant fashion, but act recessively on the cellular level as tumor suppressor genes involved in double-stranded DNA (dsDNA) break repair. Female carriers of mutations in BRCA1 or BRCA2 have a lifetime risk of breast cancer of 50%– 85%. Male carries of BRCA1 have an increased risk of breast cancer, though to a lesser degree than carriers of BRCA2 who have an estimated 5%–10% lifetime risk (Kolak et al., 2017). Additional features of the syndromes. Most notably, there is an increased risk of ovarian cancer, with an estimated lifetime risk of 10–40% for BRCA1 carriers and 10%–20% for BRCA2 carriers.

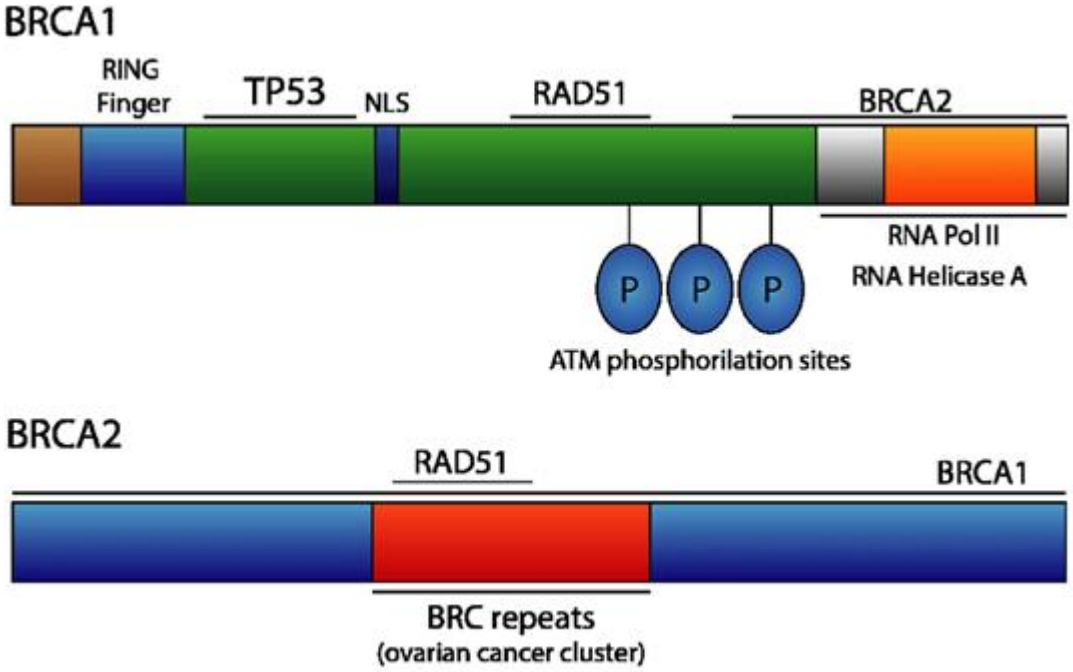


Figure 2: Schematic Representation of BRCA1 and BRCA2

Breast Self-Examination (BSE):

Breast self-examination applied as a self-method is not a sufficient, but still an important element in helping detect cancer at an early stage. It is a cheap method, generally available and does not demand any complex technical training, and can be performed in the home environment. BSE allows woman to learn about proper breast structure which helps later detect untypical lesions in mammary gland tissue. Experts from (Population Programme for Early Breast Cancer Detection (Populacyjny Program WczesnegoWykrywaniaRakaPiersi) conducted as part of a national programme to fight cancer in Poland, recommend performing breast self-examination once a month by every woman above the age of 20, preferably on the first day after the termination of menstruation (Shiovitz & Korde, 2015). Women who have undergone the menopause should also examine their breasts once in a month, preferably on the same day every month. BSE sensitivity is low (12–14%). Its disadvantage is also a high index of false positive results and over-recognition; thus, BSE should always be complemented by objective imaging examination.

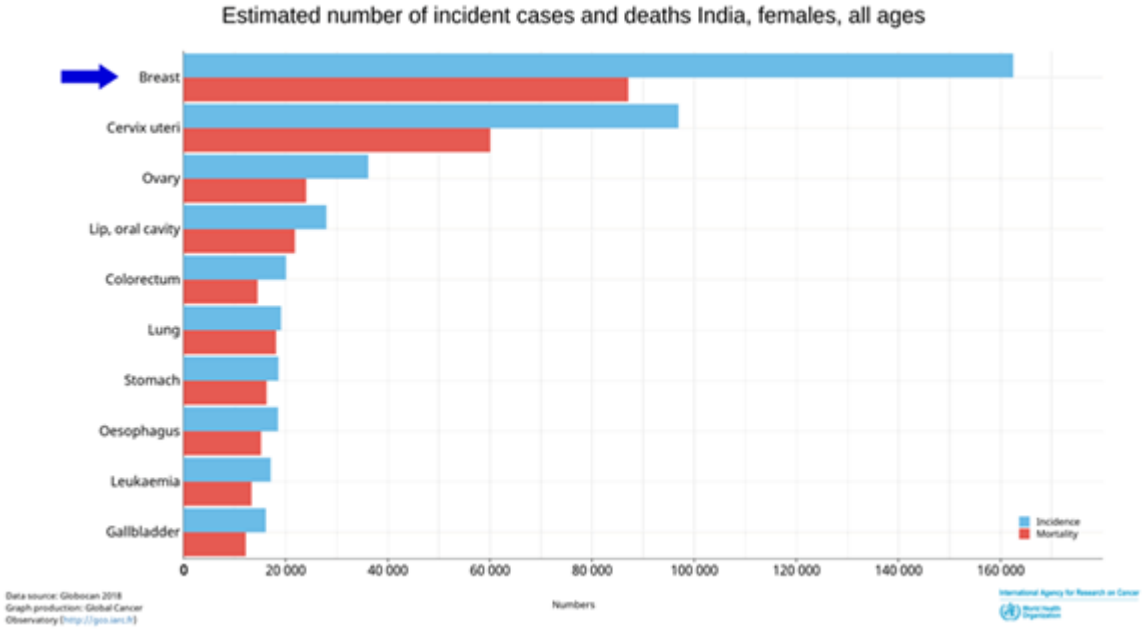


Fig2: Representation of Breast cancer in India for the year 2018.1**62, 468** women were newly detected with Breast Cancer.8**7, 090** women died of Breast Cancer For the year 2018, ratio of newly detected breast cancer cases in India, to those who died due to it is 162468 / 87090 = 1.87. For the year 2012, the ratio was 144937 / 70218 = **2.06** (Globocan 2012 data) So, roughly, in India, for every **two** women newly detected with breast cancer, one woman is dying of it.

Detecting Caner using MRI:

MRI has potential in the detection of breast cancer at early stages, when it is relatively easy to cure. Because MRI is highly sensitive for the detection of cancer, it is used as a screening method for patients who are at high risk of development of breast cancer. This recommendation also includes BRCA mutation carriers and their untested first-degree relatives, women with a history of chest irradiation between the ages of 10 and 30 years, and others with a strong family history. In addition, using breast MRI for screening populations at high risk has been found to be cost-effective; increases in cost-effectiveness have been seen with greater lifetime risk. some patients undergo MRI every 6 months as part of an institutional research cohort. Inclusion criteria for the 6-month cohort are known BRCA1 or BRCA2 carrier; lifetime risk 20% or greater according to the Contraceptive and Reproductive Experiences (CARE) study model, Tyler-Cuzick model, or Claus model when the patient has not undergone genetic testing or has a negative test result; personal history of invasive cancer before age 35 years; person`al history of ductal carcinoma in situ (DCIS) before age 35 years and first-degree relative with DCIS before age 50 or a first-degree relative with ovarian cancer; chest irradiation before age 30 years; African ancestry and first-degree relative (maternal) or second-degree relative (paternal) with breast cancer before age 40 years; and carrier of other hereditary breast cancer gene. In both groups, the patients most often have at least one of the risk factors as the reason for the study (family or genetic history, personal history of breast cancer).

Personal history of breast cancer is associated with a greater risk of a renewed cancerous lesions within the breasts. Besides, a history of any other non-cancerous alternations in breasts such as atypical hyperplasia, carcinoma in situ, or many other proliferative or non-proliferative lesions, also increases the risk significantly (Schacht et al., 2014). The histologic classification of benign lesions and a family history of breast cancer are two factors that are strongly associated with breast cancer risk.

Pathophysiology:

NSAIDs mainly block inflammation by inhibiting cyclooxygenase (COX) enzymes, leading to lower prostaglandin synthesis. Lowered levels of prostaglandins also inhibit aromatase activity, which in turn leads to lower serum estrogen levels and consequently to a decreased incidence of hormone receptor-positive tumors. The PI3K/AKT/IKK and the mitogen-activated protein (MAP) kinase pathways are involved in collagen-and prostaglandin E2 (PGE2)-induced aromatase expression. Additionally, collagen and PGE2-induced signaling pathways may crosstalk in regulating aromatase expression. Furthermore, PGE2 causes a significant decrease in p53 transcript and nuclear protein expression, as well as phosphorylation at Ser15, in primary human breast adipose stem cells. Stabilization of p53 leads to a significant decrease in PGE2-stimulated aromatase mRNA expression and activity. COX-2 concentrations are undetectable in normal breast tissue but are overexpressed in breast tumors by approximately 40%, and in ductal carcinoma in situ by as much as 80%. COX-2 expression has been associated with prostaglandin synthesis (Godet & M. Gilkes, 2017). PGE2 is considered a powerful mitogen and potential chemopreventive target. PGE2 has been shown to induce aromatase expression and de novo estrogen synthesis in breast epithelia and stromal cells in vitro; introduction of NSAIDs reduces estrogen levels in a dose-dependent manner. Because inflammation is closely associated with tumorigenesis, COX-2 has been shown to be over expressed in precancerous and malignant lesions. Its inhibition and the suppression of prostaglandin synthesis is widely accepted as the primary mechanism of the anticancer activity of NSAIDs. However, some studies have concluded that a rather COX independent mechanism may either contribute to or be exclusively responsible for the chemopreventive activity of NSAIDs (ŁUkasiewicz et al., 2021). There is limited evidence that COX-2 expression is correlated with estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and p53 expression in breast tumors. Findings of in vitro studies among human invasive breast cancer cells suggest that HER2 oncogene activation regulates COX-2 expression in breast cancer, inducing a positive feedback loop in which PGE2 in turn further induces HER2 expression. NSAIDs have been shown to reduce HER2 expression. P53 may also be associated with COX-2 expression in vitro, and animal models of breast cancer give limited evidence that p53 expression is associated with COX-2 expression (Moris et al., 2016). Additionally, it is shown that the SDF-1/CXCR4 axis is a main regulator of normal and tumor cell trafficking. Thus, it is reasonable to hypothesize that NSAIDs may interfere with SDF1 levels via the pathway COX-2 PGE SDF-1, resulting in an impairment of processes underlying metastasis development. Another possible explanation involves inflammation-induced platelet degranulation, with release of angiogenesis-regulating factors, including vascular endothelial growth factor, which can be countered by ketorolac.

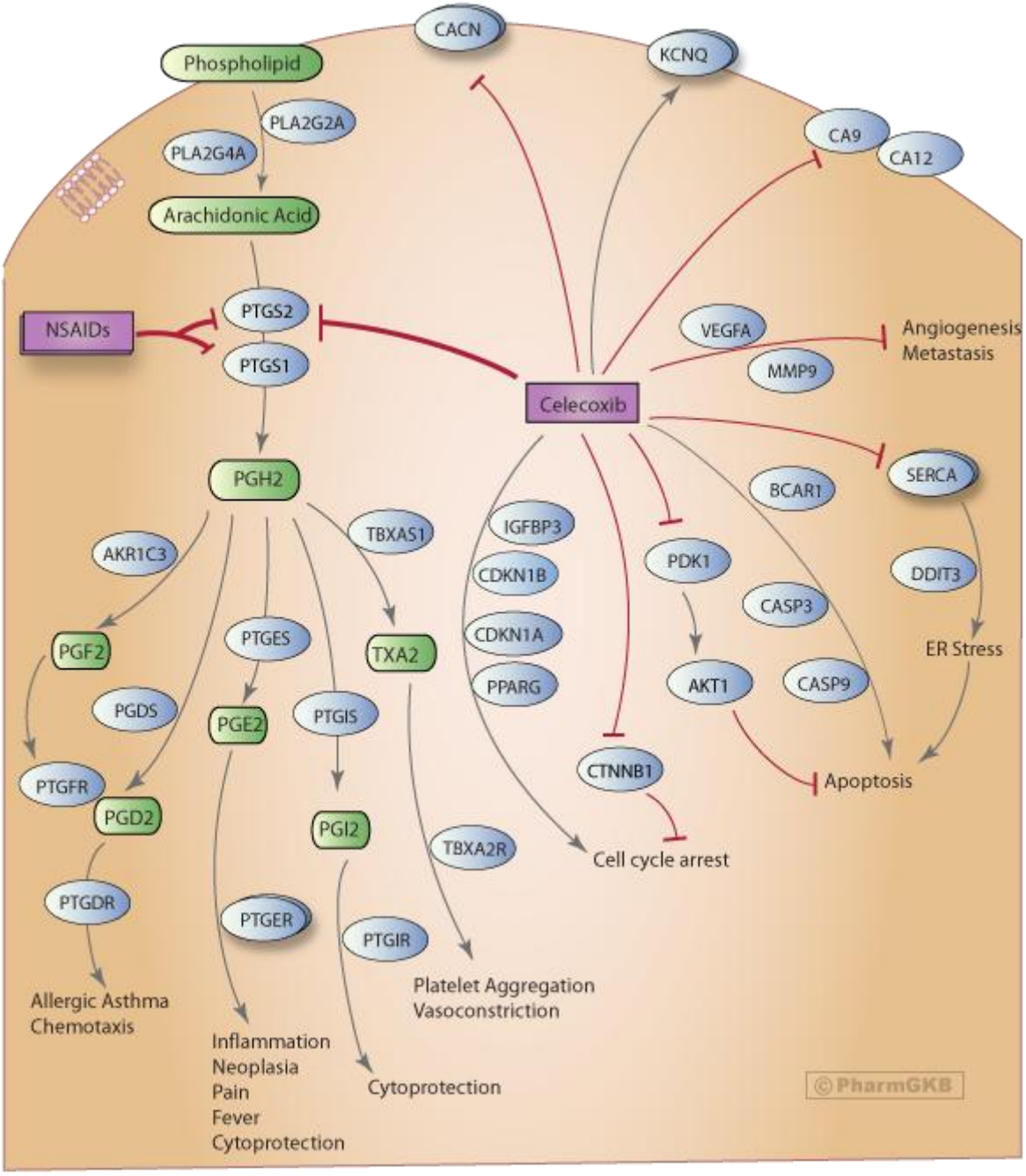
Pharmacodynamics:

Celecoxib exerts its anti-inflammatory and analgesic activities through blocking the synthesis of various inflammatory prostanoids (PG). The prostanoids, which include PGs and thromboxane, are the end products of fatty acid metabolism produced by tissuespecific COX enzymatic activity. These products are important physiological and pathological mediators that are involved in a wide range of biological processes including inflammation, pain, cancer, glaucoma, osteoporosis, cardiovascular diseases, and asthma. The production of the prostanoids (PG) is dependent on the availability of arachidonic acid (AA). Following stimulation of the cell membrane by inflammatory or mitogenic signals, the first step in PG synthesis is the release of AA from the cellular phospholipids through the action of either secretory (sPLA2, encoded by gene PLA2G2A) orcytoplasmic (cPLA2, encoded by gene PLA2G4A) phospholipases. Once AA is released, the two isoenzymes, COX-1 (encoded by PTGS1) and COX-2 (encoded by PTGS2), catalyze. NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript production of the prostanoids. As indicated above, this involves two sequential reactions. The initial COX reaction converts AA into PGG2. The second reaction reduces PGG2 to PGH2. PGH2 is then converted into active metabolites PGE2, prostacyclin (PGI2), thromboxane (T×A2), PGD2, and PGF2α by the action of tissue-specific PG synthases. These

active metabolites interact with specific prostanoid G-protein-coupled receptors to mediate diverse physiological responses, such as inflammation, fever, blood pressure regulation, clotting, and gastrointestinal protection. The COX-1 and COX-2 enzymes exhibit distinct expression profiles and roles in physiological processes. COX-1 is constitutively expressed in many cell types and is the major COX isoform in gastric tissue. It is responsible for the protection of the gastric mucosa, which led to the development of the 'COX-2 hypothesis' that drugs targeted against COX-2 only would have reduced upper gastrointestinal toxicity. Although COX-2 is highly inducible by inflammatory stimuli such as cytokines, growth factors, and tumor promoters, it is also constitutively expressed in some tissues, such as the vessel wall, the kidney, or the heart. Indeed, the depression of the physiological formation of COX-2-dependent prostanoids in these tissues has been identified as the molecular mechanism underlying the thrombotic cardiovascular complications of COX-2 inhibition. Seven placebos controlled, randomized trials with three chemically distinct pdCOX-2 inhibitors, including celecoxib, have documented the cardiovascular risk. Of note, celecoxib is now used at lower doses than in the trials that showed its cardiovascular hazard. Celecoxib has 30-fold greater inhibitory activity against COX-2 compared with COX-1, and inhibits COX-1 only minimally at therapeutic concentrations. Although the selectivity for COX-2 measured in vitro is lower for celecoxib compared with other drugs in the coxib class (e. g. rofecoxib, valdecoxib, lumiracoxib, and etoricoxib), it is very similar at therapeutic concentrations in vivo. Celecoxib also retains more ability to inhibit COX-1 compared with other coxibs; however, the consequences of this with regard to its therapeutic efficacy and toxicity are not well understood.

Antineoplastic Actions:

Selective COX-2 inhibitors, especially celecoxib, have been evaluated as a potential cancer chemopreventive and therapeutic agent in clinical trials for various malignancies. Nonselective NSAIDs such as sulindac have been used since the 1980s as adjuncts to surgery for prevention of intestinal tumors in patients with FAP, a genetic condition that often leads to colorectal cancer. Celecoxib has been shown to significantly reduce the number of colorectal polyps in patients with FAP as well as those with sporadic colorectal adenomas. Celecoxib has also demonstrated anticancer effects in established invasive tumors, including colon carcinoma, lung carcinoma, and prostate cancer, both in vitro and in vivo. The exact mechanisms for its anticancer activity are not clear and may involve both COX-dependent and COX-independent mechanisms. A wide range of tumor-associated molecular events are modulated by celecoxib in in-vitro assays, but these have yet to be placed within a coherent context that clearly describes clinical responses and most COX-independent effects were only observed at supratherapeutic concentrations in vitro; shows that the candidate genes involved in the proposed anticarcinogenic mechanisms of celecoxib include induction of apoptosis, cell cycle arrest, regulation of angiogenesis, and induction of endoplasmic reticulum (ER) stress. Celecoxib-mediated inhibition of cell cycle progression has been observed in cell culture experiments along with an increased expression of cell cycle inhibitors, p21 (encoded by gene CDKN1A) and p27 (encoded by gene CDKN1B), and/or decreased expression of cyclins (encoded by gene CCNA1, CCNB1, and CCND1). Increased degradation of the oncoprotein, β-catenin (encoded by gene CTNNB1) is also observed in celecoxibtreated human colon cancer cells, and this is associated with marked reductions in tumor cell. NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript proliferation. Again, a major caveat is that these studies were conducted at concentrations in vitro that were 10–100 times higher than plasma concentrations measured in humans. Induction of apoptosis by celecoxib is associated with activation of proapoptosis molecules such as caspases and CHOP (encoded by gene DDIT3), as well as inhibition of antiapoptotic molecules, such as PDK1 (encoded by gene PDPK1) and its downstream target AKT1. Finally, inhibition of angiogenesis and tumor cell invasiveness may also contribute to the antitumor activity of celecoxib. Celecoxib treatment decreased the expression of vascular endothelial cell growth factor and inhibition of matrix metalloproteinase 9 in cancer tissues and cell lines. Besides COX-2, celecoxib can directly bind to and inhibit a few other targets that may play important roles in the antitumor response mechanism. PDK1 is a direct target of celecoxib and inhibition of PDK1/Akt signaling correlated with celecoxib-induced apoptosis in both colon and prostate tumor cell lines. However, significantly higher concentrations of celecoxib (IC50 in micromolar range) are required for inhibition of PDK1 compared with that required to inhibit COX-2 (IC50 in nanomolar range). Celecoxib also binds to and inhibits sarcoplasmic/ER calcium ATPase. This binding can lead to rapid leakage of calcium into the cytosol, triggers ER stress, and ultimately leads to apoptosis (Gong et al., 2012). This activity is highly specific for celecoxib and has not been associated with other COX inhibitors. Carbonic anhydrases (CA), enzymes that catalyze the reversible hydration of carbon dioxide, are also inhibited by celecoxib (IC50 in the low nanomolar range). Some of the CAs (e. g. CA9 and CA12) are associated with tumor development. However, no study has clearly demonstrated the relationship between inhibition of CAs and anticancer activity of celecoxib, and celecoxib used at therapeutic concentrations also did not appear to have a clinically significant inhibitory action on renal CAs.



2. Conclusion

Woman to learn about proper breast structure which helps later detect untypical lesions in mammary gland tissue. Women who have undergone the menopause should also examine their breasts once in a month, preferably on the same day every month. Women are too shy to express their feelings to the society, so they undergone such circumstances. Awareness should be made all over the world.

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