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Preventive/Aggravating Effects of Commonly Used Drugs on Breast Cancer Progression

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Abstract

Breast cancer is the most common form of cancer among women worldwide. In the past decade increased awareness of breast cancer risk and mammography screening has led to the earlier identification of more breast cancer cases. Breast cancer incidence in developed countries is higher, however relative mortality is greater in developing countries. Studies have highlighted sedentary lifestyle, obesity, hormonal replacement therapy, reproductive history and excessive alcohol intake along with genetic factors to effect breast cancer incidence and progression in women. With changing lifestyle, use for regularly prescribed drugs including antacids, cholesterol lowering drugs, NSAIDS/anti-inflammatory drugs, laxatives, antipyretic/analgesics has seen a hike. Recent studies have linked the use of regularly prescribed drugs to the prevention and aggravation of breast cancer symptoms. Therefore, in this review we present a list of commonly prescribed drugs in relation to their preventive and aggravating effect on breast cancer.

Keywords: Breast cancer, Prevention, Estrogen-receptor negative breast cancer, Estrogen-receptor positive breast cancer, Triple negative breast cancer

1. Introduction

Breast cancer is one of the leading causes of malignancy and cancer related deaths in women worldwide [1]. According to breast cancer statistics 2017, it is the most common cancer diagnosed and leading cause of death among women in United States with about 252,710 new cases expected to be diagnosed in 2017. In India breast cancer projection during time periods 2020 suggests the number to go as high as 1797900 [2]. Breast cancer incidence in developed countries is higher, while relative mortality is greatest in developing countries [3]. Early identification of breast cancer cases have risen over the past decade following increased awareness of breast cancer risk and screening by mammography [4].

Clinical management of breast cancer has improved significantly over a last decade however managing breast cancer clinically is still difficult because of its heterogeneity [5] and 'one size' does not 'fit all'. The development of breast cancer is a multistep process beginning from benign to malignant stage, progressing and culminating in metastatic carcinoma [6]. Genetic and environmental risk factors are known to effect the incidence and progression of breast cancer. Environmental risk factors including exposure to radiation, environmental pollutants such as organochlorine pesticides are also linked to breast cancer. Animal studies have demonstrated that prolonged exposure to industrial chemicals can increase mammary tumor development [7]

Recent studies have however highlighted more risk factors including sedentary lifestyle, obesity, hormonal replacement therapy, reproductive history and excessive alcohol intake to effect breast cancer incidence and progression in women [8, 9]. This is especially important in low- and middle-income countries [LMIC] as they undergo economic transition, which includes greater mechanization of transport and labor, cultural shifts in the roles of women, and increased exposure and access to international markets. As a result, many of the lifestyle risk factors, such as tobacco use, physical inactivity, excess body weight, and reproductive patterns, which are already prevalent in high-income countries [HIC], are also becoming increasingly common in LMICs [10]. This review presents the effects of commonly prescribed drugs on breast cancer prevention or aggravation. The review also provides an insight into new mechanisms thus helping to find breast cancer treatment. [Table 1]

Table 1: Mechanism and effect of commonly used drugs on breast cancer progression

S.No.	Drugs	Affected mechanism /receptor /enzyme	Effect on breast cancer + (Preventive) - (Aggravating)	FDA approved /rejected
1.	NSAIDS Aspirin Celecoxib Rafecoxib Valdecoxib	COX2	+	Yes
2.	Metformin	Mitochondrial AMPK	+	No
3.	Statins Atorvastatin, Cerivastatin, Lovastatin, Fluvastatin, , Simvastatin, Pravastatin	(HMG-CoA) reductase inhibitors	+	Yes
4.	Chloroquine (CQ)	Autophagy inhibitor	+	Yes
5.	Omeprazole	Aryl hydrocarbon receptor (AHR) ligand	+/-	Yes
6.	Azithromycin	Antibiotic, Cytochrome P450 (CYP) 3A4 inhibitor	+	Yes
7.	Acetaminophen	Estrogenic activity	-	Yes
8.	Lisinopril	angiotensin-converting enzyme (ACE) inhibitors	-	Yes
9.	Hydrochlorothiazide	Diuretics, Removes excess salt and water	-	Yes

2. NSAIDs

Clinical and experimental studies support a preventive role for nonsteroidal anti-inflammatory drugs [NSAIDs] in breast cancer. NSAIDs are cyclooxygenase [COX] inhibitors whose isoforms are expressed in most of the cells constitutively or in response to inflammation/stimuli [11]. NSAIDs impair the formation of prostaglandins, thromboxanes and prostacyclin from arachidonic acid [12].Specifically COX-2 was found to be overexpressed in breast cancer and suggested to be the main culprit in case of mammary tumorigenesis [13]. Aspirin, which is a non-selective inhibitor of COX-1 and COX-2 have been identified to reduce the risk of breast cancer by 10% with long term use [14, 15] and overall 20 % decrease in cancer mortality among people with regular intake of aspirin, and 36% reduction in adenocarcinoma cases [14]. Celecoxib, a selective COX-2 inhibitor is the drug of choice for investigation in cancer-preventive effectiveness in preclinical and clinical studies. COX-2 has been found to be effective monotherapy in both the treatment and prevention of ER tumors and its anti-proliferative effect is dose dependent as seen from studies in the MDA-MB-241 [ER-negative] cell line [16]. Few studies have indicated the effectiveness of celecoxib in reducing mammary tumors [16-18] and some however, showed that celecoxib was unable to prevent tumor development [19]. A study by Litzenburger et al. [20] showed that celecoxib when administered along with bexarotene, a rexinoid, substantially delayed tumor development [21]. Recent Phase II and III clinical trials using celecoxib showed reduced proliferation of primary breast cancer tissues [22]. Further clinical trials to check the major concerns like toxicity, cardiovascular effects and other potential side effects associated with celecoxib use are needed to prove its significant chemopreventive effect and its use as a chemopreventive agent for breast cancer treatment.

3. Metformin [1,1-dimethylbiguanide]

Studies have shown increased incidence of breast cancer of upto 20% among postmenopausal women suffering from type 2 diabetes as compared to non-diabetic women. Also metformin, most prescribed drug for type 2 diabetes has been linked to reduced incidence of breast cancer [23]. It is a widely used drug for type 2 diabetes therapy and its primary target is mitochondrial AMP-activated protein kinase [AMPK] [24, 25]. AMPK gets activated because of mitochondrial complex 1 disruption leading increase in AMP/ATP and ADP/ATP ratios [25]. AMPK is responsible for controlling many vital metabolic processes including gluconeogenesis in liver, muscle glucose uptake and fatty acid synthesis [26]. Preventive mechanism of metformin however remains to be elusive. It has been suggested that following metformin treatment there is reduction in insulin levels which further causes reduction in cell growth, hence reduces tumorigenesis [27].

When compared to other antidiabetic therapies i.e. alpha-glucosidase inhibitors,insulin, thiazolidinediones etc; metformin particularly reduces the risk of breast cancer [20, 28-31]. In laboratory studies, using MMTV-Erb2 mice, Metformin [100 mg kg^{-1}] and Melatonin [2 mg/l] in combination inhibits mammary tumor growth depicted by delay in tumor latency by 13 % [20] and selectively targets tumor-initiating cells in this mouse model.

To further investigate the effects of metformin in breast cancer prevention, phase I and II trials were conducted [32-34]. Upon metformin administration among women with operable breast cancer a variety of biomarker changes were observed. It was found to reduce proliferation [Ki67] and increase apoptosis [TUNEL staining] in case of invasive tumor tissue [34, 35]. To further elucidate its preventive effects few clinical trials Phase II and III are in progress [20, 36, 37].

4. Statins

Statins are cholesterol lowering drugs and basically are 3-hydroxy-3-methyl-glutaryl-coenzyme A [HMG-CoA] reductase inhibitors. The statins reversibly inhibit the conversion of HMG-CoA to mevalonate thus reducing intracellular cholesterol biosynthesis [20, 38]. Commonly used statins to treat hypercholesterolemia and cardiovascular disorders are atorvastatin, cerivastatin, lovastatin, fluvastatin, simvastatin, and pravastatin. Epidemiologic, preclinical and clinical studies have provided a rationale for the evaluation

of lipophilic statins for the prevention and cure of breast cancer [38-40]. An inconsistency was indicated between relationship of statin use and incidence of breast cancer. Few studies indicated a decrease in risk of breast cancer, among statin users [38, 41-44] whereas other studies suggested its long-term use did not significantly affect risk of breast cancer [45, 46]. For the investigation of the biological effects of statins in the prevention and modulation of breast cancer biomarkers several trials have been initiated [47, 48]. Short term treatment with statins in women with high grade [DCIS or stage 1] breast cancer was found to reduce proliferation and increase apoptosis [48]. Whereas with lovastatin therapy no significant changes in breast duct cytology were seen among women with increased risk of breast cancer [49]. Therefore, in the coming future this necessitates to conduct clinical trials among high-risk populations, in particular women at high risk of Triple negative breast cancer [TNBC], to determine whether statins will be useful as preventive therapy.

5. Chloroquine [CQ]

CQ is a well-known 4-aminoquinoline class of drug widely used for malaria treatment owing to its good efficacy and minimal toxicity [50]. For more than 50 years, Chloroquine [CQ] and hydroxychloroquine [HCQ] have been used for treating malarial infections. Presence of hydroxyl group in HCQ results in decreased toxicity with no effect on its efficacy in case of malaria [51]. In last 10 years, research has repositioned CQ and related quinolone derivatives to have promising effects in cancer treatment. These can impede tumor cell proliferation and also enhance their sensitivity to chemo and radiotherapy [52]. CQ is also believed to lock cancer cell autophagy [53]. The incidence of mammary tumors and their growth rate was significantly lower and tumor onset was delayed in CQ-pre-treated rats after being subjected to mammary adenocarcinoma induction using N-methyl-N-nitrosourea [NMU] as observed by Loehberg et al. [54]. Doses of 25 and 50 mg/kg of CQ both significantly increased survival time and reduced primary tumor volume in mice implanted with a highly metastasizing breast cancer cell line, as shown by Jiang et al. [55]. Maclean et al., observed that intermittent CQ administration significantly reduced the tumor development and doubled the overall survival [OS] of Eμ-Myc mice [56].

6. Omeprazole

Omeprazole, class of proton pump inhibitors drugs is one of the most prescribed medication that can affect the functioning of metabolic transporters, enzymes and ATP-binding cassette drug-transporters [57]. It is an Aryl hydrocarbon receptor [AHR] ligand which also plays a critical role in cellular homeostasis and multiple diseases. It not only binds to endogenous biochemicals, dietary flavonoids and phytochemicals associated with health benefits but also toxicants and many pharmaceuticals [58-60]. The effects of AHR agonists/antagonists are found to be useful in case of various disease conditions including stem cell stability and expansion, different cancers and autoimmune disorders [61]. Various studies have focused on studying the molecular mechanisms involved in AHR mediated effects. An experiment was performed by Jin et al.[62] to develop selective AHR modulators [SAhRMs] towards finding a cure for ER-positive breast cancer [63, 64]. Initially he used a set of AHR active pharmaceuticals in triple-negative MDA-MB-231 cells with a primary objective to identify a known pharmaceutical that might be effective for inhibiting breast cancer metastasis. Eight different compounds were screened and among them only omeprazole was found to inhibit MDA-MB-231 breast cancer cell invasion.

Omeprazole was also found to inhibit lung metastasis of MDA-MB-231 cells in a mouse model and decreased invasion and Chemokine receptor 4 [CXCR4] expression in MCF-7 and SKBR3 breast cancer cell lines [62]. The anti-metastatic pathway was linked to decreased expression of MMP-9 and AHR-dependent suppression of the pro-metastatic gene CXCR4 treated with omeprazole. Study from Jin et al.[62] concluded that CXCR4 as one of the key target genes not only for omeprazole but also for other AHR agonists [65-68]. Downregulation of CXCR4 by omeprazole significantly contributed to its antimetastatic activity [69]. This is quite possible that required doses of omeprazole for

chemoprevention purpose will be higher than commonly used for treating acid reflux.

7. Azithromycin [AZM]

Generally antibiotics are found to be safe with minimal or no side effects with unique molecular targets against microorganisms. Several antibiotics aside from their anti-microbial activity properties, also possess an ability to induce cell apoptosis. This property of antibiotics is believed to be of importance as a potential anti-cancer drug [70, 71].
AZM is a 15-ring member macrolide antibiotic, and it differs from other macrolides known inhibitors of cytochrome P450 [CYP] 3A4 [72]. It has a unique property of rapidly accumulating and releasing slowly into cells and tissues. This ultimately results in a higher local concentration and a longer elimination half-life of the drug [73]. It exhibits anti-proliferative, inflammatory, immunomodulatory and autophagic effect finally causing apoptosis induced death in cancer cells [74-76]. Inhibitory effect of AZM on proliferation and ability to induce neutrophil apoptosis, have been suggested to contribute to its anti-inflammatory activity induced by AZM [70, 73]. However, the effect of AZM on cancer cell apoptosis and its interactions with commonly used anti-cancer agents have not been investigated yet. Miftakhova et al.[77] determined the effect of five antibiotics targeting mitochondrial function on MCF-7 cancer stem cell survival in hypoxia conditions. Interestingly, azithromycin did not show inhibiting activity on sphere formation under hypoxic condition, while number of spheres was reduced in normoxic conditions.

8. Acetaminophen

Acetaminophen is an active ingredient in many common analgesic/antipyretic medications. Acetaminophen contains a p-phenol moiety, like 17 β-estradiol, and an acetate group, like progesterone, suggesting it may have the potential to impact cells modulated by sex hormones [78]. Some exogenous compounds containing the p-phenol moiety are known to display estrogenic activity in various in vitro and in vivo systems [79]. Furthermore, the p-phenol moiety appears to be important for the estrogenic activity of these xenoestrogens [80]. Recent studies indicate that acetaminophen can stimulate proliferation of cultured human breast cancer cells and thus elicit estrogenic effects in this test system. The proliferation of three estrogen and progesterone receptor positive [ER+/PR+] breast cancer cell lines, MCF7, T47D, and ZR-75-1, was stimulated by therapeutic concentrations of acetaminophen [79].

However, acetaminophen did not stimulate the proliferation of estrogen and progesterone receptor negative [ER-/PR-] breast cancer cells, MDA-MB-231 and HS578T [79]. Furthermore, like p-nonylphenol [81], p-acetamidophenol, the p-phenolic positional isomer of acetaminophen, as compared to m- or o-phenolic isomers was found to be a more potent inducer of breast cancer cell proliferation [79]. Harnegea et al. [79] showed the involvement of ERs in acetominophen effect in breast cancer. He compared the therapeutic concentrations of acetaminophen in breast cancer cells with high ERs and cells expressing lower ERs containing T47Dco cells and determined whether acetaminophen-induced proliferation depends on ER levels or not. Secondly, he also compared two antiestrogens [ICI 182,780 and 4*-hydroxytamoxifen] and its effect on acetaminophen- induced proliferation in three human breast cancer cell lines: two ER+/PR+ [MCF7, T47D] and one ER-/PR- [MDA-MB-231]. ER binding assays in MCF7 cells were performed to determine if acetaminophen competed with estradiol for binding to ERs.

Various proliferation endpoints including percent cells in the DNA synthesis phase of the cell cycle, ^{3}H-thymidine incorporation into DNA, and cell number were monitored. It was observed that no DNA synthesis was induced in T47Dco cells, whereas in cells with high ER levels DNA synthesis was induced. This suggested that high ER levels are necessary for acetaminophen to induce proliferation. Experimental data also suggested that acetaminophen induces breast cancer cell proliferation via ERs without binding to ERs like estradiol [79]. Gadd et al. [82] tested the effect of acetaminophen on different cell lines and concluded that effect of acetaminophen on gene expression and cell proliferation is dependent more on cell type/context then on the presence of ER.

9. Lisinopril

Lisinopril is a class of angiotensin-converting enzyme [ACE] inhibitors, and has been linked with cancer risk, progression, and survival [83]. ACE inhibitors are class of medicines used to treat high blood pressure. Research by Napoleone et al. suggests that ACE inhibitors may increase the risk of breast cancer recurrence [84].

A study found that women treated for early-stage breast cancer were more than 50% more likely to have the cancer come back [recur] if they were taking an ACE inhibitor compared to women who didn't take an ACE inhibitor [85]. Research related to health histories of 1,779 women treated for early-stage breast cancer showed that among 23% of the women who at some point had taken an ACE inhibitor, a beta-blocker [another type of blood pressure medicine], or both to treat high blood pressure for more than 8 years, breast cancer was diagnosed and treated, 229 of the women had a recurrence. The researchers compared the risk of recurrence between women treated with blood pressure medicines to women who never took these medicines [85]. Compared to women never treated with blood pressure medicine: women treated with only an ACE inhibitor were 56% more likely to have a recurrence, women treated with both an ACE inhibitor and a beta-blocker were no more likely to have a recurrence, women treated with only a beta-blocker were 14% less likely to have a recurrence[85] .

10. Hydrochlorothiazide

To overcome the detrimental outcomes of hypertension including stroke, coronary artery disease, and heart failure, antihypertensive drugs [AHTs] are prescribed. Statistics indicate that AHT consumption has nearly increased 2 fold in Organization for Economic Co-operation and Development [OECD] countries from 2000 to 2011 [86]. There is a link between AHT use and breast cancer risk with the study from Heinonen et al [1990] which reported the use of rauwolfia derivatives in increasing breast cancer risk among women older than 50 [87]. Thereafter, several studies examined and studies the association between use of AHTs and breast cancer. The results obtained are conflicting and inconsistent. Hydrochlorothiazide lowers high blood pressure and also helps to prevent the occurrence of strokes, heart attacks, and kidney problems. It belongs to a class of drugs known as diuretics. This medicine helps the body to get rid of excess salts and water. It also helps to remove extra fluid accumulated in the body due to edema and other medical conditions like heart failure, liver/kidney disease. A meta-analysis study by Ni et al. [86] indicated a link between long term use of angiotensin-converting enzyme inhibitors, [ACEi]; angiotensin-receptor blockers, [ARBs] ACEi/ARB and breast cancer risk.

11. Conclusion

Breast cancer is a multifactorial disease and the most commonly diagnosed cancer in women. Epidemiology of breast cancer shows increasing trends for incidence and mortality mainly due to rapid urbanization, industrialization, population growth and ageing affecting almost all parts of the world. Cancer prevention seems to be a better strategy than treatment. With changing lifestyle and involvement of environmental factors the use of regularly prescribed drugs have seen a hike. Commonly prescribed drugs have additional effects than their prescribed action and these can be used to reduce the burden of additional drugs and treatment strategies for breast cancer. Further, some of the drugs have aggravating effects, helping breast cancer progression. Thus the effects of these drugs should be taken into account during breast cancer treatment analysis.

Conflict of Interest

The authors do not have any conflict of interest in the manuscript.

Compliance with Ethical Standards

I have read and have abided by the statement of ethical standards for manuscripts submitted to journal.

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