REVIEW

The Role of Common Pharmaceutical Agents on the Prevention and Treatment of Pancreatic Cancer

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Survival from pancreatic cancer remains poor. Conventional treatment has resulted in only marginal improvements in survival compared with survival in the previous several decades. Thus, considerable interest has emerged regarding the potential use of common pharmaceutical agents as chemopreventative and chemotherapeutic options. Aspirin, metformin, statins, β-blockers, and bisphosphonates have biologically plausible mechanisms to inhibit pancreatic neoplasia, whereas dipeptidyl-peptidase 4 inhibitors may promote it. Regardless, real-world epidemiological data remain inconclusive. This review examines the hypotheses, evidence, and current state of the literature for each of these medications and their potential roles in the prevention and treatment of pancreatic cancer. **(Gut Liver 2016;10:665-671)**

Key Words: Pancreas; Malignancy; Adenocarcinoma; Epidemiology; Aspirin; Metformin; Statins; Bisphosphonates; Beta-blockers; Dipeptidyl-peptidase 4 inhibitors

BACKGROUND

Pancreatic ductal adenocarcinoma is a lethal disease. In 2014, 46,420 cases were diagnosed in the United States, with 39,590 deaths.[1] Despite advances in surgical management and chemotherapeutic options, the 5-year survival rate has only improved slightly over the last 4 decades—from 2.4% to 6.5%.[2] Given this slow progress, efforts have been made over the last several years to explore the antineoplastic effects of commonly prescribed medications as potential adjunctive therapies for pancreas cancer. Aspirin, metformin, statins, β-blockers and bisphosphonate have all been studied to various degrees, with the hopes of repurposing them as either preventative or therapeutic agents. Dipeptidyl-peptidase 4 (DPP-4) inhibitors have received scrutiny on the opposite end of the spectrum, as possible pro-neoplastic agents. This review will examine the hypotheses, evidence, and current state of the literature of each of these medications and their possible role in the prevention and treatment of pancreatic cancer (Table 1).

ASPIRIN AND NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin have long been considered promising chemopreventative and chemotherapeutic agents due to their antioxidant and anti-inflammatory properties.[3] The major mechanism by which aspirin exerts antineoplastic effect is through inhibition of COX-1/COX-2 and modulation of the NFkB or STAT3 pathway.[4] Despite this biologic plausibility and clear association with a number of nonpancreatic cancers, the epidemiological evidence with regards to the prevention and treatment of pancreatic cancer is conflicting.

An initial case-control study of 1,149 cases and 5,952 controls found no statistically significant association between NSAID use and risk of pancreatic cancer regardless of duration of use (odds ratio [OR] <5 years, 0.8, 95% confidence interval [CI], 0.5 to 1.4; OR >5 years, 0.6, 95% CI, 0.4 to 1.1).[5] However, this study did not separate aspirin from other NSAIDs. A follow-up prospective study of 28,282 postmenopausal woman did make this distinction, and found a negative association between current aspirin use, but not NSAID use, and incident pancreatic cancer (OR aspirin, 0.47, 95% CI, 0.22 to 0.98; OR nonaspirin NSAID, 0.89, 95% CI, 0.35 to 2.24).[6] A second case-control study published several years later confirmed this result.[7] Nevertheless, data in support of the chemopreventative effects of aspirin are not entirely universal. Prospective data from the Nurses' Health Study looking at aspirin alone has suggested that woman who reported more than 20 years of aspirin use have an increased risk of pancreatic cancer (1.48; 95% CI, 1.03 to 2.43),

Table 1. Common Pharmaceutical Agents and Proposed Mechanisms in Pancreatic Cancer

Medication	Proposed effect	Mechanism of action
Aspirin	Protective	Inhibit COX-1/COX-2
		Modulate NFkB or STAT3 pathway
Metformin	Protective	Lower insulin/IGF-1 levels
		Activate AMPK which inactivates mTOR pathway
Statins	Protective	Prevent synthesis of mevalonic acid, which then activates small G proteins–Ras, Rho, and Rac
β-Blockers	Protective	Block cAMP-dependent intracellular signaling and release of EGF
		Block PKA-dependent release of VEGF
Bisphosphonates	Protective	Interfere with RAS and Rho pathways
		Inhibit tumor educated macrophages
DPP-4 inhibitors	Cancer promoting	Stimulate pancreatic β-cells to release insulin, resulting in increased α- and β-cell mass

IGF-1, insulin-like growth factor 1; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; EGF, epidermal growth factor; PKA, protein kinase A; VEGF, vascular endothelial growth factor; DPP-4, dipeptidyl peptidase-4.

although subgroup analyses limited this association to greater or equal to 14 tablets per week.[8] In order to reconcile these results, three meta-analyses have been published. Although the first two studies show no significant association between aspirin use and incident pancreatic cancer for any exposure level, the most recent analysis of 7,252 cases and 120,000 healthy controls suggests a trend towards chemoprevention for high dose but not low dose aspirin use (pooled OR high dose, 0.88, 95% CI, 0.76 to 1.01; pooled OR low dose, 0.99, 95% CI, 0.91 to 1.07).[9–11]

With regards to the chemotherapeutic potential of aspirin in pancreatic cancer, there are fewer dedicated studies. A large, pooled analysis of 25,570 patients in eight randomized trials showed a survival benefit of daily aspirin (75 mg or greater) for several common cancers including pancreatic, esophageal, lung, stomach, and colorectal. This association increased with duration of treatment.[12]

METFORMIN, DPP-4 INHIBITORS, AND THE ANTIHYPERGLYCEMICS

Metformin is a biguanide oral hypoglycemic used to treat type 2 diabetes mellitus. It is thought to work by decreasing hepatic glucose production and increasing insulin sensitivity. *In vitro* studies suggest that metformin may inhibit pancreatic cancer cells by lowering insulin and insulin-like growth factor (IGF-1) levels. These hormones may stimulate cancer cell growth via their interaction with G-protein coupled receptors.[13,14] Metformin may also have direct inhibitory effects on pancreatic ductal adenocarcinoma cells by activating the AMP-activated protein kinase (AMPK), which then inactivates proteins in the mammalian target of rapamycin pathway thereby way which promoting cell proliferation.[4,15-17]

Case-control and cohort studies have suggested that metformin use at any time may reduce the incidence of pancreatic cancer among diabetics, whereas insulin and insulin secreta-

gogues may increase this risk.[18-21] A case-control study of 973 patients with pancreatic adenocarcinoma and 863 controls found a significantly lower risk of pancreatic cancer among diabetics who had taken metformin, but an increased risk among those who had taken insulin (adjusted OR metformin, 0.41, 95% CI, 0.19 to 0.87; adjusted OR insulin, 5.04, 95% CI, 2.38 to 10.7).[19] A case-control study using the United Kingdom (U.K.) General Practice Research Database showed similar results, although the protective effect of metformin was only observed in women.[21] Data from a prospective cohort of 800,000 patients from Taiwan controlling for Charlson comorbidity score, duration of metformin exposure and use of other oral antihyperglycemics also showed a protective effect of metformin use among all diabetics (adjusted hazard ratio [HR], 0.15; 95% CI, 0.03 to 0.79).[20] Despite these results however, a recent meta-analysis of 11 studies and 1,770 pancreatic cancer cases in 730,664 diabetic patients did not find an association between metformin (adjusted OR, 0.76; 95% CI, 0.57 to 1.03), insulin, or thiazolidinediones and the risk of developing pancreatic cancer.[22] Interestingly, this meta-analysis did show a 70% increased odds of pancreatic cancer with sulfonylureas; however, significant heterogeneity was noted between studies.[22]

Few studies have examined the chemotherapeutic potential of metformin among patients with pancreatic cancer, and all of these studies have significant limitations. Another study of 302 patients with pancreatic cancer and diabetes, of which 117 were exposed to metformin, found the HR for death among diabetics with nonmetastatic disease for those on metformin to be 0.64 (95% CI, 0.48 to 0.86).[23] However, this study did not take into account the concurrent use of other antihyperglycemics or control for diabetic severity. Recall bias was a potential issue with this study, as detailed medical information was obtained via personal interview for 76% of patients. Similarly, data from a U.K. cohort of 516 diabetic patients with stage IV pancreatic cancer (247 of whom were exposed to metformin) found no

difference in survival on univariate or multivariate survival analysis (HR, 1.09; 95% CI, 0.80 to 1.47); however, this study was unable to control for race or account for insulin or other antidiabetic agents.[24]

Another class of antihyperglycemic that has received considerable attention for its possible association with incident pancreatic cancer is the DPP-4 inhibitors. These medications inhibit the breakdown of the incretin hormones, glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP), which in turn lower blood glucose concentrations by stimulating pancreatic β-cells to release insulin.[25] Sitagliptin was the first DPP-4 inhibitor earning Food and Drug Adminstration (FDA) approval in 2006, and several other newer drugs have since been developed. Initial enthusiasm for these medications was diffused by early studies suggesting a possible increase in pancreatitis and pancreatic cancer among diabetics receiving incretin-based therapies. Pancreatitis is a well-known risk factor for pancreatic cancer.[26] Not only did preclinical studies in animal models suggest increased β-cell mass and regeneration, but autopsy studies in humans reports a fourfold increase in α- and β-cell mass among diabetics receiving these therapies compared to those on other therapies.[27-29] An examination of the FDA's database of reported adverse events found a 6-fold increased odds of pancreatitis among those taking sitagliptin (OR, 6.74; 95% CI, 4.61 to 10.00) compared to other diabetic medications and 10-fold increase in the odds of pancreatitis among those taking GLP-1 mimetic exenatide (OR, 10.68; 95% CI, 7.75 to 15.10).[30] Both drugs also appeared to significantly increase the risk of pancreatic cancer without increasing the risk of other cancers. Nevertheless, two subsequent large multicenter placebo controlled clinical trials (EXAMINE and SAVOR-TIMI) as well as a meta-analysis found no increased rate of acute or chronic pancreatitis with DPP-4 inhibitor therapy.[31-33] Most recently, the FDA and the European Medicines Agency (EMA) published a joint statement on the association between incretin-based drugs and both pancreatitis and pancreas cancer. After exhaustive review of both preclinical and epidemiological studies, the authors conclude that current data do not support a causal relationship between DPP-4 inhibitors and either pancreatitis or pancreatic cancer.[34]

STATINS

Statins are 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors indicated for the treatment of hypercholesterolemia and the primary and secondary prevention of coronary heart disease and its risk equivalents.[35] Statins have pleiotropic effects, and their use as antineoplastic agents has been of considerable interest for several reasons. First, HMG-CoA inhibition prevents the synthesis of mevalonic acid, a precursor of nonsteroidal isoprenoids, which then activate small G proteins such as Ras, Rho, and Rac.[36] Ras signaling is particularly important in pancreatic tumorigenesis.[37-39] Second, statins are antiangiogenic and exert proapoptotic and anti-inflammatory effects.[40-43] To date, statin use has been associated with a decreased risk for a number of cancers, including colorectal, esophageal, liver, and pancreatic cancer.[44-46]

Similar to other commonly prescribed medications, dedicated epidemiological data on statins and the risk of pancreatic cancer are conflicting. A large case-control study of 483,733 predominantly U.S. male (98.5%) veterans found that statin use for more than 6 months was associated with a 67% risk reduction in incidence of pancreatic cancer (adjusted OR, 0.33; 95% CI, 0.26 to 0.41), whereas statin use for more than 4 years was associated with an 80% risk reduction (adjusted OR, 0.20; 95% CI, 0.13 to 0.29).[47] However, a subsequent meta-analysis of 12 studies (three randomized placebo-controlled trials [RCTs], four cohorts, and five case-control studies) found no evidence of association between statin use and pancreatic cancer among either the RCTs (relative risk [RR], 0.99; 95% CI, 0.44 to 2.21) or the observational studies (RR, 0.86; 95% CI, 0.60 to 1.24).[48] Although no publication bias was detected, there was high heterogeneity among the observational studies and sex-specific analyses were not performed. One way to reconcile these data is the notion that the inverse association between statins and incident pancreatic cancer may be gender-specific. This position is supported by two further more recent observational studies. A smaller U.K. based case-control study found a reduced risk of pancreatic cancer only among male smokers (OR, 0.11; 95% CI, 0.01 to 0.96), and a larger San Francisco clinic based case-control study of 536 cases and 869 controls found a similar sex-specific inverse association in males only (OR for men, 0.50, 95% CI, 0.32 to 0.79; OR for women, 0.86, 95% CI, 0.52 to 1.43).[49,50]

Statins may also have a chemotherapeutic use after pancreatic cancer diagnosis. A recent population based analysis of the Surveillance, Epidemiology and End Results (SEER)-Medicare database found a 21% reduced risk of death (HR, 0.79; 95% CI, 0.67 to 0.93) for statin use after diagnosis among patients with low-grade (I or II), but not high grade (III or IV) pancreatic adenocarcinoma.[51] Patients who had undergone pancreatectomy, had chronic pancreatitis, and had not been treated with a statin prior to cancer diagnosis were also found to benefit from post-diagnosis statin therapy. Finally, there is emerging clinical trial investigating the role of statins as adjunctive chemotherapeutic agents in pancreatic cancer. Although a randomized, double-blinded, placebo-controlled phase II trial of gemcitabine and simvastatin versus gemcitabine and placebo found no additional clinical benefit to statin therapy in advanced pancreatic cancer patients, no increased toxicity was noted either.[52] As such, there may be a role for statin therapy in conjunction with anti-epidermal growth factor receptor (anti-EGFR) agents such as erlotinib or cetuximab, or even as part of neo-adjuvant regimens in less advanced disease, although further studies are needed to investigate these possibilities.

β-BLOCKERS

β-Blockers are a widely used class of drugs employed for the treatment of heart failure, hypertension, myocardial infarction, and arrhythmias among other disorders. β-Blockers competitively antagonize the β-1 or β-2 adrenergic receptor, which subsequently results in decreased intracellular levels of cyclic adenosine monophosphatase (cAMP).[53] B1 receptors are primarily found in heart muscle, whereas B2 receptors are primarily found in the bronchus or smooth muscle of the peripheral vasculature.

A number of *in vitro* studies have suggested a potential role of β-blockade in the regulation of several cancers, including pancreatic, prostate, breast, colon, and ovarian.[54-58] With regards to pancreas cancer, β-adrenergic agonists stimulate human ductal adenocarcinoma cell growth via adenyl cyclase, which has downstream effects on cAMP, protein kinase A (PKA), and phosphorylation of cyclic AMP response element binding protein (p-CREB).[54,59] PKA also activates the EGFR pathway. Furthermore, tobacco, via the carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), may also stimulate pancreatic cell growth via this same β-adrenergic mechanism.[54,60] In an animal model of hamsters with ethanol-induced pancreatitis, the nonselective β-blocker propranalol showed strong antineoplastic effect, inhibiting upregulation of the α7 nicotinic acetylcholine receptor (α7nAChR) as well the extracellular signal regulated protein kinases (ERK1/2), p-CREB, EGF, and vascular endothelial growth factor.[54]

No dedicated epidemiological studies have examined the effects of β-blockade on pancreatic cancer incidence or survival. However, a retrospective study of the U.K. primary care Doctors' Independent Network database examining patients with several cancers found an effect opposite to that suggested by *in vitro* studies. Among patients with pancreatic and prostate cancer, those on β-blockers had worse overall survival than those on other antihypertensive medications (HR pancreatic cancer, 1.88; 95% CI, 1.09 to 3.25).[61] Nevertheless, a subsequent study of the parallel Clinical Practice Research Datalink found no such effect of β-blocker use among patients with pancreatic cancer (HR, 1.04; 95% CI, 0.92 to 1.08).[62]

BISPHOSPHONATES

Bisphosphonates inhibit osteoclast-mediated bone resorption, and are indicated for the prevention and treatment of osteoporosis. The prescribing of bisphosphonates has increased substantially in Western countries over the last 2 decades, especially in older women.[63,64] A number of preclinical studies suggest a potential role of bisphosphonates as antineoplastic agents against a wide variety of cancers, and several clinical trials have explored the role of these medications as adjuvant therapy in breast cancer.[65-67] In pancreatic cancer cells in particular,

bisphosphonates have been shown to induce antiproliferative, antiapoptic, and antimetastatic effects via interference with the RAS and Rho pathways and the inhibition of tumor educated macrophages.[68-71]

There is minimal epidemiological data on the association between bisphosphonate use and incident pancreatic cancer. A case-control study of 41,826 patients from the U.K. general practice database found a reduced incidence of all cancer after any bisphosphonate use (HR, 0.87; 95% CI, 0.82 to 0.92), however no statistically significant reduction in risk of pancreatic cancer (HR, 0.91; 95% CI, 0.53 to 1.35).[72] A large nested-case control study of two other large U.K. databases compromising 180,000 cases (matched with 1:5 with controls) however, did find an inverse association between bisphosphonate use and incident pancreatic cancer (adjusted OR, 0.79; 95% CI, 0.68 to 0.93) when both cohorts were combined.[73]

To date, no clinical trials or epidemiological studies have explored the chemotherapeutic role of bisphosphonates in patients with pancreatic cancer. However, early data suggest that the combination of zoledronic acid and gemcitabine may inhibit proliferation and invasion of pancreatic cells *in vitro*, and tumor growth and the development of liver metastases in athymic mice with implanted pancreatic cancer cell lines.[74]

CONCLUSIONS

Survival from pancreatic cancer remains exceedingly poor. Conventional treatment has resulted in only marginal improvements in survival over the last several decades. As such, screening and prevention have taken a prominent role in the approach to the management of this disease. Specifically, the medical community has focused considerable attention on the re-purposing of common pharmaceutical agents as possible chemopreventative and chemotherapeutic options. Aspirin, metformin, statins, β-blockers and bisphosphonates all have biological plausible mechanisms to inhibit pancreatic neoplasia, whereas DDP-4 inhibitors may promote it. Unfortunately, epidemiological evidence in support of these hypotheses remains moderate at best. Aspirin, but not NSAIDs, may have slightly reduced risk of incidence pancreatic cancer, but not to a clinically relevant degree. Metformin may reduce the risk of pancreatic cancer in diabetics, but data from observational studies and meta-analyses are conflicting. With regards to survival, metformin does not appear to benefit diabetics with advanced disease; however, its role in locoregional disease and in nondiabetics as a possible chemopreventative agent remains unknown. Statins appear to exert a weak, but not insignificant male-specific protective effect on incident pancreatic cancer for unclear reasons. The role of statins as adjunctive chemotherapeutic agents is currently being studied. β-Blockers have strong *in vitro* and animal data to suggest a protective effect, but the few population studies performed have not supported this hypothesis. With regards

to bisphosphonates, large population studies have shown only minimal associations with incident pancreatic cancer, and the potential chemotherapeutic role of this class, though biologically promising, remains untested at present. Finally, although early data suggested an increased risk of pancreatitis and pancreatic cancer with incretin-based therapies (DPP-4 inhibitors and GLP agonists), more recent clinical trials, meta-analytical data, and a combined FDA/EMA statement argue against any causal relationship.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article are reported.

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