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Chemoprevention strategies for pancreatic cancer

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Abstract

Pancreatic cancer has a poor prognosis and it is often diagnosed at advanced stages, which makes it very difficult to treat. The low survival rate of patients with pancreatic cancer points toward an increased need for novel therapeutic and chemopreventive strategies and early detection. Increased consumption of fruits and vegetables has been associated with a reduced risk of pancreatic cancer. Both synthetic as well as natural, diet-derived bioactive compounds have been evaluated as pancreatic cancer chemopreventive agents and have been shown to have various degrees of efficacy in cellular and *in vivo* animal models. Some chemopreventive agents (for example curcumin, resveratrol, B-DIM) have also been reported to sensitize pancreatic cancer cells to standard chemotherapeutic drugs (for example gemcitabine or erlotinib), which suggests the potential use of chemopreventive agents as potentiators of standard chemotherapy. Very few clinical trials with pancreatic cancer chemopreventive agents have been completed and some are in early phases. Further development of pancreatic cancer chemopreventive agents may prove to be tremendously valuable for individuals at high-risk of developing pancreatic cancer and patients who present with premalignant lesions. This Review discusses the current state of the pancreatic cancer chemoprevention field and highlights the challenges ahead.

Introduction

Despite important progress in the treatment of pancreatic cancer, the survival rate of patients with this disease has not significantly improved over the last few decades. Pancreatic cancer is the fourth leading cause of cancer-related deaths in the USA, with a 5-year survival rate of less than 5%.¹ In 2009 it was estimated that in the USA alone 42,470 men and women would be diagnosed with pancreatic cancer, and 35,240 people would die from this disease.¹

Owing to their genetic predisposition, members of pancreatic-cancer-prone families, including those with a history of Peutz-Jeghers syndrome, hereditary pancreatitis and familial atypical multiple mole melanoma (FAMMM), are at the highest risk of developing pancreatic cancer.^{2,3} Other factors associated with an increased risk of developing pancreatic cancer include advancing age, tobacco smoking, a family history of the disease, chronic pancreatitis, type II diabetes, obesity, and a high dietary intake of fried foods and red meat.²⁻⁷ Several epidemiological studies have reported that increased consumption of fresh fruits and vegetables is associated with a reduced risk of pancreatic cancer,² although other studies have reported null results.⁸

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Competing interests

The authors declare no competing interests.

Pancreatic cancer is often diagnosed at an advanced stage and it is highly resistant to conventional chemotherapy and radiation therapy, which makes it very difficult to treat. Gemcitabine and erlotinib represent the current FDA approved standard chemotherapy for pancreatic cancer, but produce only a modest survival benefit in patients with advanced disease.⁹⁻¹³ The low survival rate of patients with pancreatic cancer points toward an increased need for novel therapeutic, early detection, and chemoprevention strategies. This Review discusses the current state of the pancreatic cancer chemoprevention field and highlights the current strategies and challenges for chemoprevention of pancreatic cancer.

Pathogenesis of pancreatic cancer

Pancreatic cancer is generally thought to arise from pancreatic ductal epithelial cells, although acinar cells may also be a source of pancreatic neoplasia.^{14,15} In addition, other differentiated or progenitor/stem cells have also been suggested as potential cells of origin for the development of pancreatic cancer.¹⁶ For instance, insulin-expressing endocrine cells of the adult pancreas have been shown to transdifferentiate and give rise to exocrine neoplasia under conditions of chronic pancreatic injury.¹⁶ The progression from normal epithelium to pancreatic cancer is associated with the accumulation of several genetic mutations, and seems to gradually evolve via precursor lesions, called pancreatic intraepithelial neoplasias (PanINs). Activation of the oncogene *KRAS* and inactivation of tumor suppressor genes—for example *p16* (also known as *CDKN2A*), *SMAD4* (also known as *DPC4*), and *p53* (also known as *TP53*)—are common events in the development of pancreatic cancer.¹⁴ *KRAS* mutations occur very early in the development of pancreatic cancer and are the most frequent mutations associated with pancreatic adenocarcinoma (found in 75–90% of patients with pancreatic cancer).^{5,17,18} Activating mutations in the *KRAS* gene occur both in pancreatic ductal adenocarcinoma and in the early precursor lesions (PanINs), and increase in frequency with disease progression.^{14,15} Epidermal growth factor (EGF), hepatocyte growth factor (HGF), and insulin-like growth factor 1 (IGF-1) and their corresponding receptors are also frequently overexpressed in pancreatic cancer.¹⁹⁻²¹

The main signaling pathways and the molecular pathogenesis of pancreatic cancer have been reviewed by Wong and Lemoine in 2009.⁹ The survival pathway phosphatidylinositol-3-kinase (PI3K)-Akt is frequently activated in many cancers, including pancreatic cancer. The PI3K-Akt pathway is activated in approximately 60% of pancreatic cancers⁹ and represents a prognostic indicator for pancreatic ductal adenocarcinoma.²² Constitutive activation of the signal transducer and activator of transcription 3 (STAT3) pathway is frequently detected in pancreatic cancer and may contribute to increased growth, angiogenesis and metastasis of pancreatic cancer.^{23,24} Nuclear factor kappa B (NF-κB) controls different biological processes, such as inflammation, cell cycle and apoptosis, and is a key antiapoptotic transcription factor in pancreatic ductal adenocarcinoma.²⁵ NF-κB activation has been reported in pancreatic cancer cells, in animal models of pancreatic cancer, and in human pancreatic tissue.^{26,27}

Pancreatic cancer is associated with chronic inflammation. Overexpression of inflammatory markers, such as cyclooxygenase 2 (COX-2), inducible nitric oxide synthase (iNOS), 5-lipoxygenase (5-LOX), and elevated levels of C-reactive protein are associated with poor survival of patients with pancreatic cancer.^{4,28} Disruption of Notch and Hedgehog signaling pathways, which are important during embryonic development, has been reported in the pathogenesis of pancreatic cancer.²⁹ The Notch signaling pathway is relatively inactive in normal adult pancreatic tissue, but shows moderate to high activity in metaplastic ductal epithelium, PanIN-2, and pancreatic ductal adenocarcinoma tissue.^{15,29} Active Notch signaling can synergize with *KRAS* to induce the formation of PanINs.¹⁵ Activation of the

Hedgehog signaling pathway has been implicated in the initiation of pancreatic ductal neoplasia and exhibits a graded increase in late-stage lesions and pancreatic carcinomas.³⁰

Chemopreventive agents

Chemoprevention refers to the use of agents that have the potential to prevent or delay the development of cancer. Cancer chemopreventive agents are mainly intended to be used in people who are at high risk of developing cancer or who present with premalignant lesions. A cancer chemopreventive agent must be nontoxic to normal tissue so that it can be safely administered to cancer-free, high-risk patients. Ideally, a chemopreventive agent should have specific targets that are highly expressed in cancer cells or premalignant lesions but not in normal tissue. Natural and synthetic compounds have both been evaluated as cancer chemo-preventive agents. These compounds can either target a single specific pathway (mainly the synthetic compounds) or several pathways in carcinogenesis (mainly the natural compounds). The development of chemopreventive agents includes the performance of rigorous cellular and animal studies followed by clinical trials.

Several natural and synthetic compounds have been evaluated as chemopreventive agents for pancreatic cancer. Figure 1 illustrates the effect of potential pancreatic cancer chemopreventive agents on multiple pathways involved in the pathogenesis of pancreatic cancer. Agents developed primarily as cancer chemopreventive agents have also been proposed for chemo-therapy, either as stand-alone drugs or as sensitizers to standard chemotherapeutic drugs (Tables 1 and 2).

Curcumin

Curcumin (diferuloylmethane) is a bioactive component of turmeric, which is a spice derived from the rhizome of the plant *Curcuma longa* (commonly known as turmeric). Curcumin has been extensively studied over the last few decades and is known to have numerous biological activities.^{31,32}

Cellular studies have demonstrated that curcumin inhibits the proliferation of pancreatic cancer cells and suppresses the activation of NF- κ B.^{33,34} RelA, the p65 subunit of NF- κ B, is constitutively activated in approximately 67% of human pancreatic adenocarcinomas, but not in normal pancreatic tissues.³³ Wang *et al.* showed that curcumin inhibits RelA-DNA binding activity and potentiates apoptotic cell death induced by paclitaxel in MDAPanc-28 pancreatic cancer cells.³³ In other studies, curcumin was reported to suppress COX-2 and epidermal growth factor receptor (EGFR) expression and inhibit ERK1/2 activity in P34 pancreatic cancer cells.^{35,36} Curcumin also downregulates the Notch signaling pathway (through crosstalk between Notch and NF- κ B signaling pathways) in association with inhibition of cell growth and induction of apoptosis in BxPC-3 and PANC-1 pancreatic cancer cells.³⁷ In a study by Sun *et al.*, curcumin was reported to alter specific microRNA (miRNA) expression in BxPC-3 human pancreatic cancer cells, upregulating miRNA-22 and downregulating miRNA-199a*.³⁸ Upregulation of miRNA-22 was associated with downregulation of two of its target genes, the transcription factor SP1 and the estrogen receptor 1 protein (ESR1), which is also expressed by pancreatic cancer cells.³⁸

In combinational chemotherapy studies, curcumin has been reported to sensitize pancreatic cancer cells to gemcitabine,^{34,36} celecoxib³⁹ and paclitaxel³³ (Table 1). In an orthotopic animal model in which human pancreatic cancer cells (MiaPaCa-2) were implanted in the pancreas of athymic nude mice, curcumin (1g/kg, once daily by mouth) enhanced the antitumor activity of gemcitabine (25 mg/kg, twice weekly, intraperitoneal injection) by inhibiting cell proliferation, angiogenesis and NF- κ B-regulated gene products (cyclin D1, Bcl-2, Bcl-xL, c-myc, COX-2, and survivin).³⁴ Swamy *et al.* showed that the combination

of 0.2 % curcumin with 15% fish oil (high in *n*-3 fatty acids) acts synergistically to inhibit pancreatic cancer cell growth in a xenograft model (BxPC-3) of pancreatic cancer in association with downregulation of proinflammatory proteins COX-2, 5-LOX, iNOS, and upregulation of cyclin-dependent kinase inhibitor p21.⁴⁰

Curcumin has a low bioavailability, but is well tolerated (up to 8 g/day) without showing dose-limiting toxicities.⁴¹⁻⁴³ Oral administration of 4–8 g of curcumin results in peak plasma levels of 0.41–1.75 $\mu\text{mol/l}$.³¹ Although free plasma levels may not reflect tissue levels, *in vitro* studies suggest that microgram levels are required for activity in pancreatic cancer.³¹ To increase the bioavailability of curcumin, three synthetic curcumin analogues, FLLL11 and FLLL12⁴⁴ and difluoro compound CDF,⁴⁵ have been synthesized and found to be more effective than curcumin in inhibiting cell viability and inducing apoptosis in pancreatic cancer cells *in vitro*. To enhance curcumin absorption, Li *et al.* encapsulated curcumin in liposomes and administered these intravenously for systemic delivery.⁴⁶ The authors found that liposome-encapsulated curcumin (40 mg/kg, three times per week) inhibited the growth of BxPC-3 and MiaPaCa-2 human pancreatic cancer cells in nude mice xenografts by inducing apoptosis and suppressing angiogenesis.⁴⁶

Several clinical trials with curcumin in patients who have pancreatic cancer are currently in progress (Table 2). Curcumin is being used either alone or in combination with gemcitabine or NSAIDs. In a phase II trial of curcumin (8 g daily), which is still ongoing, the results for the first 25 patients included in the study have been published and show that curcumin is well tolerated and has biological activity in some patients with advanced pancreatic cancer.⁴⁷ Circulating curcumin was detected in glucuronide and sulfate conjugate forms at low levels (steady-state level at day 3 was 22–41 ng/ml), which confirms its poor oral bioavailability.⁴⁷ Despite these suboptimal plasma levels, a biological effect was observed following administration of curcumin, with downregulated expression of NF- κ B, COX-2, and p-STAT3 in peripheral blood mononuclear cells of patients with pancreatic cancer.⁴⁷

COX-2 inhibitors

Cyclooxygenases (COXs) are enzymes that are responsible for the conversion of arachidonic acid to prostaglandins. COX-2 is an isoform of COXs and is induced in response to growth factors, cytokines and tumor promoters.⁴⁸ In normal pancreatic tissue COX-2 is detected only in islets cells, and not in acinar or ductal cells.⁴⁸ COX-2 is overexpressed in pancreatic cancer⁴⁹⁻⁵¹ and therefore represents a specific target for pancreatic cancer treatment and prevention.

Several COX-2 inhibitors have been evaluated for the treatment and/or prevention of pancreatic cancer. Celecoxib is a selective COX-2 inhibitor that has been shown to prevent *N*-nitrosobis (2-oxopropyl) amine (BOP)-induced pancreatic cancer in Syrian hamsters⁵² and to significantly reduce tumor growth in pancreatic cancer xenografts in athymic nude mice.⁵³ Celecoxib was shown to suppress vascular endothelial growth factor (VEGF) gene expression by suppressing SP1 transcriptional activity and to reduce angiogenesis and metastasis in pancreatic cancer in *in vitro* and *in vivo* studies.⁵⁴ Lev-Ari *et al.* showed that the combination of celecoxib with curcumin had a synergistic effect in inhibiting the growth of pancreatic cancer cells expressing COX-2.³⁹ In another study, Mukherjee *et al.* showed that the combination of celecoxib with a novel Mucin-1 (MUC1) -based vaccine and low-dose chemotherapy (gemcitabine) was effective in preventing the progression of PanINs to invasive pancreatic ductal adenocarcinomas in a transgenic Kras^{G12D} animal model that expresses human MUC1 as a self molecule.⁵⁵

A phase II trial of gemcitabine in combination with celecoxib (400 mg twice a day) has been conducted, but the results are inconclusive and suggest that higher doses of celecoxib may

be necessary to achieve significant antitumor activity.⁵⁶ A phase III trial of gemcitabine, celecoxib and curcumin is currently in progress.⁵⁷

Other (COX-2 specific and non-specific) NSAIDs, including aspirin, nimesulide, etodolac, sulindac, indomethacin, phenylbutazone and NS398, have been evaluated for the prevention and/or treatment of pancreatic cancer and have shown efficacy in cellular and animal models.^{50,51,58-60} For example, Funahashi *et al.* evaluated the efficacy of the selective COX-2 inhibitor nimesulide in preventing the progression of PanINs in a conditional Kras^{G12D} mouse model.⁵⁸ Nimesulide-treated animals had significantly fewer PanIN-2 and PanIN-3 lesions and reduced intrapancreatic prostaglandin E₂ levels compared with control animals.⁵⁸ Takahashi *et al.* showed that the NSAIDs indomethacin and phenylbutazone significantly reduce pancreatic cancer development in a hamster model of BOP-induced pancreatic cancer.⁶⁰

The results of epidemiological studies evaluating the association between aspirin use and pancreatic cancer are inconsistent. In a prospective study conducted by Anderson *et al.*, aspirin use was associated with a lower risk of pancreatic cancer (relative risk [RR] 0.57, 95% CI 0.36–0.90, $P = 0.005$) in postmenopausal women living in Iowa during 7 years of follow-up.⁶¹ In another prospective study conducted by Schernhammer *et al.*, an extended period of regular aspirin use was associated with an increased risk of pancreatic cancer in women in the US Nurses' Health Study.⁶² Women who reported more than 20 years of regular aspirin use had an increased risk of pancreatic cancer (RR 1.58, 95% CI 1.03–2.43, $P = 0.01$).⁶²

Green and black teas

Green and black teas are derived from the plant *Camellia sinensis* (unfermented and fermented, respectively), and contain a series of polyphenols that act as powerful antioxidants. In a cellular study, epigallocatechin-3-gallate (EGCG), the major polyphenol extracted from green tea, has been shown to suppress human pancreatic carcinoma cell growth and invasion.⁶³ Lyn-Cook *et al.* demonstrated significant inhibition of cell growth *in vitro* in human pancreatic cancer cells treated with black and green tea extracts, a mixture of green tea polyphenols, and the purified polyphenols epicatechin-3-gallate and EGCG, in association with decreased expression of the *KRAS* gene.⁶⁴

In animal models, oral intake of a 0.1% solution of green tea catechins has a protective effect against the oxidative stress induced by BOP in the pancreas of Syrian hamsters by reducing the tissue concentration of lipid peroxides and the amount of 8-hydroxydeoxyguanosine in nuclear DNA.⁶⁵ In another study, green tea polyphenols significantly reduced hyperplasia and the total number of duct lesions induced by BOP in Syrian hamsters when used either alone or in combination with palm carotene.⁶⁶

Several case-control and prospective studies have examined the association between tea consumption and pancreatic cancer risk, with varying results. Increased tea consumption was associated with a decreased risk of pancreatic cancer in some studies,⁶⁷⁻⁷⁰ while others found no association between tea intake and pancreatic cancer risk.⁷¹⁻⁷⁶ No clinical trials on the effect of tea extracts or purified tea polyphenols against pancreatic cancer have been reported so far, although the chemopreventive effects of green tea extracts are currently being investigated in clinical trials of lung, breast and prostate cancer.⁵⁷ Phase I pharmacokinetic studies of two green tea polyphenol formulations (EGCG and polyphenon E) revealed that in general they are well tolerated by healthy individuals, with mild adverse effects.^{77,78} Peak plasma EGCG levels of 0.4–0.8 $\mu\text{mol/l}$ were achieved after the administration of these formulations at doses equivalent to the EGCG content of 8–16 cups of green tea.^{77,78}

β-carotene

β-Carotene is a carotenoid that is found in many yellow and red fruits and vegetables, and in dark green, leafy vegetables. β-carotene inhibits the development of BOP-induced pancreatic cancer in Syrian hamsters; Majima *et al.* demonstrated a decrease in pancreatic hyperplasia and reduced numbers of carcinomas and ductal lesions after treatment with β-carotene, palm carotene (containing 60% β-carotene, from palm oil), and the combination of palm carotene with lower doses of green tea polyphenols.⁶⁶ Another study by Appel *et al.* evaluated the effect of β-carotene on the development of acinar pancreatic lesions induced by azaserine in rats.⁷⁹ Rats administered a diet high in β-carotene or selenium developed fewer pancreatic tumors than control rats. The same study also reported fewer atypical acinar cell nodules and adenocarcinomas in rats that received vitamin C; no effect was observed with vitamin E.⁷⁹

The effect of β-carotene on pancreatic cancer in humans was evaluated in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study.⁸⁰ This study randomly allocated 29,133 Finish male smokers aged 50–69 years to one of the following intervention groups: dl-α-tocopherol (a form of vitamin E), β-carotene, a combination of dl-α-tocopherol and β-carotene, or placebo. Patients received daily supplements for 5–8 years. The incidence of pancreatic carcinoma was 25% lower among men who received β-carotene supplements compared with those who did not, although the difference was not statistically significant.^{80,81}

Vitamin D

Cellular and animal studies have shown that analogues of 1α,25-dihydroxyvitamin D₃, the biologically active form of vitamin D, exhibit inhibitory activity against pancreatic cancer cell growth *in vitro* and *in vivo*.⁸² Kawa *et al.* showed that vitamin D analogues inhibit pancreatic cancer cell growth by inducing cell cycle arrest in the G₀/G₁ phase, inhibiting the production of cyclins D1, A and E, and upregulating the expression of cyclin-dependent kinase inhibitors p21 and p27.⁸³ In preclinical *in vivo* studies, vitamin D analogues were shown to inhibit the growth of pancreatic cancer cells in xenograft models in athymic nude mice.^{83,84}

Epidemiological studies investigating the effect of vitamin D on pancreatic cancer in humans have reported inconsistent results. In an analysis of two prospective studies conducted by Skinner *et al.* in the cohorts of the Health Professionals Follow-up Study and the Nurses' Health Study, a high dietary intake of vitamin D was associated with a reduced incidence of pancreatic cancer.⁸⁵ Individuals consuming ≥600 international units (IU) of vitamin D daily had a 41% lower risk of developing pancreatic cancer compared with those who consumed <150 IU daily.⁸⁵ However, in a prospective, nested case-control study conducted by Stolzenberg-Solomon *et al.* in the Alpha-Tocopherol Beta-Carotene Cancer Prevention cohort of male Finish smokers, a high prediagnostic serum concentration of 25-hydroxyvitamin D (25[OH]D; the circulating form of vitamin D) was associated with an increased risk of pancreatic cancer (highest versus lowest quintile, >65.5 versus <32.0 nmol/l; odds ratio [OR] 2.92, 95% CI 1.56–5.48, *P* = 0.001).⁸⁶ In a more recent nested case-control study conducted by Stolzenberg-Solomon *et al.* in the Prostate, Lung, Colorectal and Ovarian Screening Trial cohort, prediagnostic serum 25(OH)D levels were not associated with the overall risk of pancreatic cancer. However, a positive association with risk of pancreatic cancer was observed among individuals with low estimated annual solar UVB exposure, but not among those with moderate to high UVB annual exposure.⁸⁷ A phase II clinical trial with the vitamin D analogue seocalcitol (EB1089) in patients with advanced pancreatic cancer showed no objective antitumor activity.⁸⁸

Vitamin E

Vitamin E has been shown to inhibit the growth of pancreatic cancer cell lines in some⁸⁹ but not all⁹⁰ studies. Alpha-tocopherol was shown to inhibit carcinogenesis in a number of animal models, as reviewed by Kelloff *et al.*⁹¹ However, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study showed a trend towards an increase in the incidence of pancreatic carcinoma and a high rate of mortality in patients receiving vitamin E supplements, although this trend was not statistically significant.^{80,81} Stolzenberg-Solomon *et al.* performed a cohort analysis of the effect of vitamin E intake (including four tocopherols and four tocotrienols) and serum levels of α -tocopherol on exocrine pancreatic cancer in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study. The authors found that high serum α -tocopherol concentrations were associated with a low risk of pancreatic cancer (highest compared with lowest quintile, hazard ratio 0.52, 95% CI 0.34–0.80, $P = 0.03$).⁹² The inverse association between serum α -tocopherol concentration and pancreatic cancer was more pronounced in individuals who had a high intake of polyunsaturated fat.

Farnesyl transferase inhibitors

Disruption of the *RAS* signaling pathway by farnesyl transferase inhibitors has been proposed as a chemoprevention strategy.⁹³ Farnesyl transferase inhibitors (such as perillyl alcohol, dlimonene, farnesol and geraniol) have been evaluated as chemopreventive agents for pancreatic cancer in cellular and animal models of disease.^{94–97} The inhibitory activity of perillyl alcohol, geraniol and farnesol in pancreatic cancer cells is associated with induction of cell cycle arrest at the G0/G1 phase and an increase in the levels of cyclin-dependent kinase inhibitors p21 and p27.⁹⁷ Perillyl alcohol has also been reported to induce Bak-dependent apoptosis in pancreatic cancer cells while nonmalignant cells were not affected.⁹⁵

A pilot phase II clinical trial of perillyl alcohol demonstrated some biological effects of this agent in patients with pancreatic cancer. Patients who received full perillyl alcohol treatment (288 ± 32 days) had a longer survival compared with those who did not receive full treatment (204 ± 96 days), although the difference was not statistically significant.⁹⁸ There was also a trend towards an increased level of apoptosis in patients who received perillyl alcohol compared with control patients.

Isothiocyanates

Isothiocyanates are compounds that are found naturally as thioglucoside conjugates (glucosinolates) in cruciferous vegetables (such as broccoli, cabbage, cauliflower, kale and Brussels sprouts).⁹⁹ The isothiocyanate sulforaphane has been studied extensively as a cancer chemo-preventive agent for several types of cancer. Kallifatidis *et al.* showed that treatment with sulforaphane alone or in combination with TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) reduces the growth of pancreatic tumors that are rich in tumor initiating cells or cancer stem cells by suppressing NF- κ B activity, cell proliferation and tumor angiogenesis, and by inducing apoptosis.¹⁰⁰ The treatment did not exhibit marked cytotoxic adverse effects on normal pancreatic cells. Treatment with two other chemopreventive agents—resveratrol and wogonin—also sensitized pancreatic tumor initiating cells to TRAIL-induced apoptosis, although to a lesser extent than sulforaphane.¹⁰⁰

Other isothiocyanates, such as benzyl isothiocyanate and phenethyl isothiocyanate, are also reported to have growth inhibitory activity against pancreatic cancer in cellular and animal models of disease. For example, benzyl isothiocyanate has been shown to inhibit the growth of human pancreatic cancer cells *in vitro* and in xenograft models of pancreatic cancer by

inducing apoptosis and causing cell cycle arrest at the G2/M phase.¹⁰²⁻¹⁰⁴ Treatment with phenethyl isothiocyanate inhibits BOP-induced pancreatic tumors in Syrian hamsters.^{105,106}

Other potential chemopreventive agents

Several other natural or synthetic compounds have been evaluated as pancreatic cancer chemopreventive agents and showed some efficacy in preclinical cellular and/or animal studies. For example, genistein—an isoflavonoid found in soy products—has been shown to induce apoptosis and inhibit NF- κ B activation in BxPC-3 pancreatic cancer cells via Notch-1 and NF- κ B signaling pathways, and to sensitize pancreatic cancer cells to docetaxel and cisplatin.^{107,108} Furthermore, El-Rayes *et al.* showed that genistein potentiates the effect of erlotinib in BxPC-3, AsPC-1 and Capan-2 pancreatic cancer cells through inhibition of Akt and NF- κ B.¹⁰⁹ Resveratrol, a polyphenol found in grape skins, was shown to inhibit the growth of pancreatic cancer cells and enhance the antitumor activity of gemcitabine in an orthotopic mouse model.^{110,111} Capsaicin, the major pungent ingredient of red chili peppers, was shown to inhibit cell viability and induce apoptosis in BxPC-3 and AsPC-1 pancreatic cancer cells via generation of reactive oxygen species and disruption of mitochondrial membrane potential, and to suppress the growth of AsPC-1 cells in a xenograft model of pancreatic cancer.¹¹² 3,3'-diindolylmethane (DIM) is an acid condensation product of indole-3-carbinol (I3C), which is found in cruciferous vegetables. DIM, as well as its more bioavailable analogue BDIM, inhibits cell growth and induces Par-4 apoptosis in L3.6pl and Colo-357 pancreatic cancer cells.¹¹³ Pretreatment with B-DIM sensitized L3.6pl, Colo-357 and BxPC-3 pancreatic cancer cells to gemcitabine and cisplatin through activation of Par-4 induced apoptosis and inactivation of the Akt signaling pathway.¹¹³ In another study, B-DIM was shown to potentiate the effect of erlotinib in BxPC-3 cells *in vitro* and in an orthotopic model of pancreatic cancer with BxPC-3 cells.¹¹⁴ The combination of B-DIM and erlotinib was much more effective as an antitumor agent compared with either agent alone.¹¹⁴

Metformin, which is a drug that is widely prescribed for the treatment of type 2 diabetes, has been shown to prevent the development of BOP-induced pancreatic cancer in Syrian hamsters,¹¹⁵ and to inhibit the growth of pancreatic cancer cells (MiaPaca2 and PANC-1) in xeno-graft models in athymic nude mice.¹¹⁶ An epidemiological study showed a protective effect of metformin against pancreatic cancer in patients with type 2 diabetes.¹¹⁷ Treatment with metformin was associated with a 62% lower risk of developing pancreatic cancer compared with metformin non-use (OR 0.38, 95% CI 0.22–0.69, $P = 0.001$).¹¹⁷ This study suggests that metformin could be used as a preventive strategy against pancreatic cancer in a subset of patients with type 2 diabetes. This finding warrants further confirmation in larger studies.

Clinical recommendations for prevention

To date, the best preventive strategy against pancreatic cancer is risk reduction, including smoking cessation, weight reduction, a diet high in fruits and vegetables, and regular exercise.^{118,119} Although several natural and synthetic agents are under development as potential chemopreventive agents for pancreatic cancer, currently there are no clinical recommendations for prevention of pancreatic cancer using pharmacological agents. Although beneficial effects are not consistently reported in all studies, the most promising evidence for chemoprevention exists for vitamin D, curcumin and, to a lesser extent, for aspirin (short-term use only). Effort is being made at the preclinical level to identify new chemopreventive agents and define their mechanisms of action. No definitive clinical recommendations can be made until further randomized clinical trials and observational studies are conducted.

Several obstacles must be overcome in order to develop chemopreventive agents for pancreatic cancer. One such challenge is developing potential surrogate markers that can be used to demonstrate that a particular chemopreventive agent is effective. Although precursor lesions such as advanced PanINs have been identified, these lesions cannot be reliably detected without histological analysis of resected pancreatic specimens. Thus, it is essential to find novel approaches, such as molecular imaging or a biomarker that is correlated with these lesions. Defining potential surrogate end point markers could also reduce the number of patients needed and the time required to perform high quality pancreatic cancer chemoprevention trials.

Emphasis also needs to be placed on defining which individuals have a high risk of developing pancreatic cancer—in whom the benefits associated with a chemoprevention strategy will outweigh any possible risks. Our center, along with others, is exploring sophisticated modeling techniques that incorporate clinical, demographic and genetic information to create risk stratification models for pancreatic cancer development. Presently, the only group of patients who would be candidates for a chemoprevention trial would be unaffected members from pancreatic-cancer-prone families, although chemoprevention strategies might prove to be useful as early interventions in patients who present with premalignant lesions or at the early stages of carcinogenesis.

Combinational chemoprevention seems to be a promising strategy for enhanced chemopreventive action through synergistic effects of multitarget agents combined on the basis of detailed understanding of their mechanisms of action. Enhanced delivery methods (for example use of liposomal curcumin) could also increase the circulation levels of chemopreventive agents that have low bioavailability. Several chemopreventive agents are currently being tested in clinical trials for lung, prostate, breast and colon cancer; once completed the results might provide useful information for designing pancreatic cancer chemoprevention trials.

Conclusions

Pancreatic cancer has a poor prognosis, and the survival rate of patients with pancreatic cancer has not substantially improved over the last few decades. Several natural and synthetic compounds have been evaluated as pancreatic cancer chemopreventive agents and have been shown to have various degrees of efficacy in cellular and *in vivo* animal models. Mechanistic studies suggest that many natural cancer chemopreventive agents could act as multitarget agents affecting several pathways in pancreatic carcinogenesis. Chemopreventive agents have also been reported to potentiate the effect of standard chemotherapeutic drugs (such as gemcitabine or erlotinib), demonstrating the potential use of chemopreventive agents in the realm of standard chemotherapy. Very few clinical trials with potential pancreatic cancer chemopreventive agents have been completed and some are in early phases. Definitive, large-scale, randomized, clinical trials are necessary to determine the clinical efficacy of promising pancreatic cancer chemopreventive agents.

The success of any chemopreventive strategy will depend on defining the underlying mechanisms of action of the cancer chemopreventive agents through rigorous preclinical research combined with improvements in our ability to identify premalignant lesions and develop surrogate end point markers for clinical trials. Chemoprevention may prove to be tremendously valuable for individuals who are at a high risk of developing pancreatic cancer—including individuals with known risk factors for pancreatic cancer and patients who present with pre-malignant lesions.

Review criteria

PubMed was searched in October 2009 for English-language publications using the terms: “pancreatic cancer”, “chemoprevention”, “prevention”, “antioxidant therapy”. Articles were selected on the basis of their relevance, and additional articles were identified from their reference lists. Reviews have been cited when appropriate to limit the number of references. The website <http://www.clinicaltrials.gov> was used to identify ongoing pancreatic cancer-related clinical trials with chemopreventive agents.

Key points

- Pancreatic cancer has a low survival rate, which has not improved in the last few decades; current chemotherapeutic treatment is not effective
- A great deal of research interest has been directed towards evaluating natural and synthetic chemopreventive agents in cellular and animal models of pancreatic cancer
- Very few pancreatic cancer clinical trials with chemopreventive agents have been completed; more trials are in early phases
- Pancreatic cancer chemopreventive agents could be useful in individuals who are at high risk of developing cancer or who present with premalignant lesions
- Pancreatic cancer chemopreventive agents have also a potential use as potentiators of standard chemotherapy

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Figure 1.
Examples of molecular targets of chemopreventive agents in pancreatic cancer

Table 1

Chemopreventive agents as potentiators of chemotherapeutic drugs in preclinical studies of pancreatic cancer

Chemopreventive Agent	Chemotherapeutic Drug	System	Reference
Curcumin	Gemcitabine	<i>in vitro</i> + orthotopic	34,36
Curcumin	Celecoxib	<i>in vitro</i>	39
Curcumin	Paclitaxel	<i>in vitro</i>	33
Celecoxib + Mucin-1-based vaccine	Gemcitabine	Kras ^{G12D} /MUC1 model	55
Sulforaphane	TRAIL	<i>in vitro</i> + xenograft	100
Genistein	Docetaxel, Cisplatin	<i>in vitro</i>	107
Genistein	Erlotinib	<i>in vitro</i>	109
Resveratrol	Gemcitabine	<i>in vitro</i> + orthotopic	111
B-DIM	Gemcitabine, Cisplatin	<i>in vitro</i>	113
B-DIM	Erlotinib	<i>in vitro</i> + orthotopic	114

Table 2

List of ongoing clinical trials with pancreatic cancer chemopreventive agents

Trial	Site	Objective	Reference
Curcumin (in advanced pancreatic cancer)	MD Anderson Cancer Center, USA	Phase II Published trial for first 25 patients (biological effect in some patients)	NCT00094445* 47
Curcumin + gemcitabine (in advanced pancreatic cancer)	Rambam Health Care Campus, Israel	Phase II	NCT00192842*
Curcumin + gemcitabine + celecoxib (in advanced pancreatic cancer)	Tel-Aviv Sourasky Medical Center	Phase III	NCT00486460*
Curcumin	Kyoto University, Japan	Phase II	31
Celecoxib (prevention in patients with premalignant pancreatic lesions)	Indiana University School of Medicine, USA	Phase II	NCT00198081*
Vitamin E Delta-Tocotrienol (resectable pancreatic cancer)	H. Lee Moffitt Cancer Center and Research Institute, USA	Phase I	NCT00985777*
Genistein (resectable pancreatic cancer)	Jonsson Comprehensive Cancer Center at UCLA, USA	Phase II	NCT00882765*

* Source: www.clinicaltrials.gov