Review

Vitamin D and Pancreatic Cancer—An Update

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Received: 7 December 2010; in revised form: 30 December 2010 / Accepted: 31 December 2010 / Published: 6 January 2011

Abstract: The non-classical actions of vitamin D, namely anti-proliferation, pro-differentiation, immune function modulation, and anti-inflammation, have received great attention during the past decade, in particular, the potential of vitamin D analogs alone or in combination with other anticancer agents for the treatment of a variety of cancers. The association between vitamin D status and the higher incidence of many forms of cancer has suggested that vitamin D may play a role in the etiology of these types of cancer. Although it is still controversial whether this association exists for pancreatic cancer, biochemical evidence clearly indicates pancreatic cancer cells are responsive to the inhibitory effect of vitamin D and its analogs. In this review, we discuss briefly the origin and current therapy of pancreatic cancer, the history, source, metabolism and functions of vitamin D, the recent progress in the epidemiological studies of sunlight, and vitamin D status, and biochemical studies of vitamin D analogs in the prevention and treatment of pancreatic cancer.

Keyword: vitamin D; pancreatic cancer; prevention; treatment; vitamin D receptor; chemoprevention; adenocarcinoma

1. Introduction

Pancreatic adenocarcinoma (PCA) is one of the most lethal human malignancies. Among the most common causes of cancer-related mortality, PCA ranks fourth in the Western countries and fifth
worldwide [1]. In the U.S., 37,680 new cases of PCA were identified and 34,290 died from this disease in 2008 [2]. The almost 1:1 ratio of incidence to mortality clearly indicates a poor prognosis and the lethal nature of PCA, which is attributable to difficulty of early diagnosis, early local spread, distant metastasis and resistance to traditional chemotherapy and radiotherapy. The overall five-year survival rate is estimated to be in the range of 1–4%, which is much lower than the other types of cancers, such as colon, breast and prostate cancers [1]. Up to the present time, surgical extirpation has been the choice of treatment. However, the overall five-year survival rate after resection is only about 10–29% [3-5]. Moreover, at the time of presentation, 40% patients already had distant metastasis and another 40% were diagnosed with locally advanced cancer [1,2,6], which excluded them from being good candidates for resection.

Although the definite causes of pancreatic cancer still remain poorly understood, several environmental factors have been implicated. Among them, the use of tobacco has been linked to an increase in the incidence of pancreatic cancer from abundant epidemiological studies conducted since 1966 [7]. It has been reported that smokers have a greater chance of developing pancreatic cancer than nonsmokers and the risk increases with increasing frequency and length of tobacco exposure [8]. After cessation of cigarette smoking for 10 years or longer, the risk of pancreatic cancer dwindles [9]. Albeit, alcohol has been implicated as a risk factor for several types of cancers, such as the cancers of liver and esophagus, the association between alcohol and pancreatic cancer is less convincing [10,11]. A pooled analysis of 14 cohort studies reported a positive relationship between pancreatic cancer and alcohol consumption in women consuming more than 30 g of alcohol per day [12]. High caloric intake and obesity are also found to be risk factors for pancreatic cancer [13-16]. Nevertheless, fruits and vegetables failed to offer any protective benefit for pancreatic cancer in a large-scaled cohort study [17]. Others, like intake of coffee, use of aspirin, previous cholecystectomy, and history of diabetes or chronic pancreatitis, may be contributing factors for pancreatic cancer as well, although less conclusive [18-20].

While investigating the incidence of pancreatic cancer in different locations, an interesting geographical variation has been observed, that is in northern latitudes, the incidence of pancreatic cancer is three- to four-times higher than that in areas closer to equator [21]. This finding has been attributed to sunlight or ultraviolet (UV) B exposure, which is directly related to vitamin D synthesis in humans. Epidemiologic studies have shown that vitamin D status, influenced by living at high or low latitude, solar UVB exposure and dietary intake of vitamin D, is inversely associated with the incidence of some cancers such as prostate, colon and breast [22-24].

Recently, due to the dismal outcome of available chemotherapy and radiotherapy for pancreatic cancer, some new regimens or strategies have been developed for the treatment of pancreatic cancer. Here, we describe the current advances in the understanding of pancreatic cancer etiology, recent controversy on the relation between sunlight, vitamin D and pancreatic cancer incidence, the potential use of vitamin D analogs for the prevention and treatment of pancreatic cancer, and a brief history, metabolism and functions of vitamin D.

2. The Origin of Pancreatic Cancer and Current Therapy

Pancreatic cancer originates from the pancreatic ductal epithelium. The disease is believed to evolve from premalignant lesions to invasive cancer, combined with successive accumulation of various gene
mutations during the progressive process [25]. The premalignant lesions include pancreatic intraepithelial neoplasia (PanINs), intrapancreatic mucinous neoplasia and mucinous cystic neoplasia, with PanINs being the most common and best characterized histological precursor of pancreatic cancer [26,27]. PanINs lie in small (less than 5 mm) pancreatic duct, and consist of columnar to cuboidal cells containing mucins [28,29]. Fourrier classifications are used to describe PanINs, which are PanINs-1A, PanINs-1B (low grade PanINs and refer to as flat and papillary type, respectively), PanINs-2 (intermediate grade PanINs ), and PanINs-3 (high grade PanINs ), to reflect its sequentially evolutionary process to pancreatic cancer. During the progression from low to high grade PanINs, accumulation of gene mutations is observed, which includes up-regulation of the oncogene KRAS2 [30] and down-regulation of tumor-suppressor genes, such as CDKN2A [31], TP53 [32], and DPG 4 [33]. Besides originating from premalignant lesions, pancreatic cancer may derived from a subgroup of about 1–5% of cells with stem cell properties [34,35]. Through unlimited self-renewal and asymmetric division, these pancreatic cancer stem cells lead to more un-differentiated cells. In addition, due to chemotherapy- and radiotherapy-resistant properties of pancreatic cancer stem cells, treatment of pancreatic cancer has become very difficult. Currently, the standard treatment for resectable pancreatic cancer remains surgery. However, only 20% of PCA patients are surgically operable [1,2,6]. After operation, adjuvant chemotherapy with either gemcitabine or a combination of fluorouracil and leucovorin is able to improve progression-free period and overall survival [36-38]. Combination of adjuvant chemotherapy and radiation therapy seems to increase overall survival; however, the results are not significant [39]. For unresectable pancreatic cancer, the principle of treatment is mainly palliative. The standard chemotherapy for this group of patients is gemcitamine alone [40].

3. Role of Vitamin D in Cancer Treatment

3.1. History of Vitamin D

In 1822, Sniadecki noted that children living on farms had a lower prevalence of rickets compared to the children who lived in the city of Warsaw, Poland. In 1889, Theodore Palm, a medical missionary and epidemiologist, observed that children living near equatorial areas did not have rickets and suggested sunbathing as a possible cure and strategy for rickets prevention. They both attributed their finding of geographic differences in rickets incidence to varied exposures to sunlight [41,42]. In 1918, Edward Mellanby kept dogs indoors and fed them with oats exclusively, which successfully made the animals rachitic, and this disease could be cured by cod liver oil. During that period, cod liver oil was known to treat night blindness and fracture. Mellanby did not know whether the cure of rickets was due to the newly discovered vitamin A present in cod liver oil [43] or a new substance. It was not until 1922 that McCollum clearly demonstrated that the anti-rachitic principle present in cod liver oil was a new substance and named it “vitamin D” [44]. Around the same period, Huldshinsky in 1919 discovered that children with rickets could be cured by exposure to sunlight [45]. So, there seemed to be some close relationship between sunlight exposure and vitamin D. Steenbock and Black [46] then noted that UV-irradiated food could cure rickets, which led to a great discovery later that UV light was capable of transforming one substance stored in food and skin to another form. In other words, UV light could produce vitamin D, which possesses anti-rachitic activity.
3.2. Source and Metabolism of Vitamin D

The sources of vitamin D for humans includes exposure to sunlight, food, and vitamin D supplement. Among them, exposure to sunlight is responsible for about 90% of vitamin D requirement [47]. Vitamin D has two forms: vitamin D2 and vitamin D3. Vitamin D2 is mainly synthesized from ergosterol of yeast and vitamin D3 is produced from 7-dehydrocholesterol of lanolin. When human skin is exposed to UV irradiation (wavelength 290–315 nm), 7-dehydrocholesterol, stored in the basal and suprabasal layers of skin [48,49], is photolyzed to form previtamin D3, which is then thermoisomerized to vitamin D3 [47,50,51]. Either vitamin D3 or ingested vitamin D2 enters the blood circulation and is carried by vitamin D binding protein (DBP) to other organs, such as the liver. In the liver, vitamin D (representing vitamin D2 and vitamin D3) is further converted to 25-hydroxyvitamin D [25(OH)D] catalyzed by vitamin D-25-hydroxylase (25-OHase) [52]. Serum 25(OH)D, the index of vitamin D status in humans, has even higher affinity for DBP than vitamin D, and therefore is also bound to DBP in the circulation. 25(OH)D is then further hydroxylated by 25(OH)D-1α-hydroxylase (1α-OHase or CYP27B1) in the kidneys to form 1α,25-dihydroxyvitamin D [1α,25(OH)2D], which is the most biologically active form of vitamin D. Both 25(OH)D and 1α,25(OH)2D can be hydroxylated by 25(OH)D-24-hydroxylase (24-OHase or CYP24A1) to form their corresponding 24-hydroxylated metabolites. Hydroxylation at carbon 24 of the vitamin D molecule by 24-OHase is the first step of the inactivation process for vitamin D [52]. However, it is now established that 1α-OHase and 24-OHase are expressed in many tissues and cells [52-54], including the expression of 1α-OHase in the pancreas [55,56]. Thus, the pancreas has the ability to active and inactivate vitamin D in an autocrine/paracrine fashion [55].

3.3. Functions of Vitamin D

1α,25(OH)2D exerts its hormone-like functions through binding to vitamin D receptor (VDR), an endocrine member of the nuclear receptor superfamily [57] to regulate its target genes (Figure 1). A study, in which a Chip-sequencing method was applied to define genome-wide mapping of VDR binding, reported that VDR was bound to 2,776 genomic sites in 229 vitamin D-regulated genes [58]. Since VDR was first identified in 1979 in many tissues not known for regulating calcium and bone metabolism [59], it is not surprising that 1α,25(OH)2D may possess functions beyond its originally identified action on calcium homeostasis and bone mineralization. It is now well-established that 1α,25(OH)2D exhibits anti-proliferative, pro-differentiating, anti-inflammatory, and pro-apoptotic activities in a tissue- and cell-specific manner [55,60-62] and, so far, it has been shown to have growth inhibitory effect on prostate, colon, breast, lung, liver and pancreatic cancer cells, which express VDR [47,63-67].
Figure 1. Vitamin D sources, metabolism, mechanism of action and biological activities. Vitamin D₃ (cholecalciferol) is either derived from the diet, including supplements, or synthesized in the skin via sunlight exposure (290-315 nm) from the precursor 7-dehydrocholesterol (7-DHC). Vitamin D₃ is initially hydroxylated in the liver by vitamin D-25-hydroxylase (25-OHase) to generate the circulating prohormone 25-hydroxyvitamin D₃ [25(OH)D₃]. The subsequent conversion of 25(OH)D₃ to the active form, 1α,25-dihydroxyvitamin D₃ [1α,25(OH)₂D₃], occurs in the kidneys catalyzed by a tightly regulated enzyme 25(OH)D-1α-hydroxylase (1α-OHase or CYP27B1). However, the activation may take place in many extra-renal tissues, including pancreas, bone, breast, colon, prostate, etc. The extra-renal synthesis of 1α,25(OH)₂D may be one reason why serum 25(OH)D level, instead of the circulating level of the active form, 1α,25(OH)₂D, is the index of vitamin D nutritional status. The resulting 1α,25(OH)₂D₃ elicits its transcriptional effects by binding to the vitamin D receptor (VDR)/retinoid X receptor (RXR) complex on vitamin D response element (VDRE) in the promoter region of vitamin D responsive genes. The cellular effects include anti-proliferation, pro-differentiation, pro-apoptosis, anti-inflammation, immune response regulation, etc. In addition to 25-OHase and 1α-OHase, 24-OHase (CYP24A1) also plays an important role in the vitamin D metabolic cascade, and thereby, in the regulation of vitamin D actions. The primary role of 24-OHase is to hydroxylate 1α,25(OH)₂D₃ and 25(OH)D₃ to their corresponding 24-hydroxylated metabolites, the first step of vitamin D catabolic pathway to inactivate VDR ligands.
3.4. Vitamin D and Pancreatic Cancer

As mentioned in Section 3.3, 1α,25(OH)2D3 possesses anti-tumor activity through anti-proliferative, pro-apoptotic, and pro-differentiation actions in a cell- and tissue-specific manner [60-62,64]. Regarding pancreatic cancer, 1α,25(OH)2D3 has been shown to up-regulate the expression of p21 and p27 and down-regulate the expression of cyclins A, D1, and E, leading to cell cycle arrest at G0/G1 phase [68]. However, 1α,25(OH)2D3 is known to cause hypercalcemia and hypercalciuria side effects. To overcome these lethal side effects caused by systemic administration of 1α,25(OH)2D3, several thousands of less calcemic or noncalcemic analogs of 1α,25(OH)2D3 have been synthesized and studied in vitro and in vivo animal models. Some of them have been found to have more potent anti-tumor activity mediated by cell-cycle arrest, stimulating differentiation, and/or promoting apoptosis on pancreatic cancer cells in vitro and in the xenograft animal model [68-73]. One of these analogs, EB-1089, has been investigated in a phase II clinical trial to treat advanced pancreatic cancer. However, the trial showed that the analog failed to prolong the survival of patients significantly [74]. In a recent published phase II clinical trial enrolling 25 advanced pancreatic cancer patients, a combination of oral 1α,25(OH)2D3 (0.5 µg/kg) and docetaxel significantly increased the period of time-to-progress of pancreatic cancer as compared to treatment by docetaxel alone [75]. Recently, a VDR-alkylating derivative of 1α,25(OH)2D3, 1α,25-dihydroxyvitamin D3-3-bromoacetate (1α,25(OH)2D3-3-BE), has been studied in vitro and was shown to inhibit the growth of several pancreatic cancer cell lines to a greater extent than 1α,25(OH)2D3 [56,76]. The in vitro activity was further accentuated by combining with 5-amino-imidazole-4-carboxamide-1-beta-4-ribofuranoside (AICAR) [76]. Furthermore, a new vitamin D analog, 19-nor-2α-(3-hydroxypropyl)-1α,25(OH)2D3 (or MART-10) has been shown to be about 1000-fold more active than 1α,25(OH)2D3 in inhibiting the proliferation of several prostate cancer cell lines in vitro [67,77]. Most importantly, MART-10 does not increase serum calcium in animals [78]. Furthermore, MART-10 is more resistant to 24-hydroxylase-mediated degradation pathway and has a lower binding affinity for DBP compared to 1α,25(OH)2D3, suggesting that this analog would be more bio-available than 1α,25(OH)2D3 in circulation [67,77]. Given the poor prognosis and little effective therapeutic options against pancreatic cancer, these two new analogs are promising candidates for further pre-clinical studies, and subsequent clinical trials for pancreatic cancer patients.

3.5. Epidemiological Studies of Vitamin D and Pancreatic Cancer

Vitamin D status, as determined primarily by solar UVB exposure and dietary intake of vitamin D, has been shown to positively impact on the incidence of prostate, colon and breast cancers in a number of epidemiological studies [22-24]. For pancreatic cancer, two earlier epidemiologic studies published in 2006 reported an inconsistent relationship between pancreatic cancer incidence and vitamin D status [79,80]. However, the death rate of pancreatic cancer has been found to be inversely associated with sun exposure [81-84]. Two recent pooled nested case-control studies conducted by Stoleznberg-Solomon et al. failed to confirm the inversed association between circulating concentration of 25(OH)D and risk of pancreatic cancer [85]. However, the same group did confirm a positive association among subjects with low estimated annual residential solar UVB exposure and pancreatic cancer risk [85]. The lack of association between serum 25(OH)D levels and pancreatic cancer risk could be due to that the study utilized a single serum sample obtained years prior to diagnosis for 25(OH)D
measurement. It may well be that serum 25(OH)D changed over the years after the measurement. For example, Yin et al. conducted case-control studies with zero lag time between diagnosis and serum 25(OH)D measurement, not nested studies, and found an inverse correlation between serum 25(OH)D level and breast cancer [86]. Furthermore, Stoleznberg-Solomon et al. showed that a high 25(OH)D level exceeding 100 nmol/L (40 ng/mL) would have a two-fold increase in pancreatic cancer incidence (odds ratio = 2.12, 95% confidence interval: 1.23, 3.64) [87]. On the contrary, a report by Mohr SB et al. demonstrated an inverse association between UVB irradiation and incidence rates of pancreatic cancer worldwide. They also found that incidence rates were half as high in countries with estimated serum 25(OH)D > 30 ng/ml than in those with ≤ 30 ng/mL [88]. Some other studies also showed inverse relationships between UVB and pancreatic cancer [89-91]. Results from investigating the association of insulin and glucose levels and the development of pancreatic cancer have also indicated a positive association between high insulin and glucose levels and pancreatic cancer [92-95]. Since vitamin D is capable of regulating the synthesis, binding and actions of insulin [96-98], the finding may imply that an inverse relationship between pancreatic cancer incidence and vitamin D status could exist. Due to these contradictory findings, more careful studies with consideration of the impacts of different genotypes of VDR, DBP, and CYP enzymes (vitamin D hydroxylases) and other possible genomic variance, and environmental factors on vitamin D metabolism and functions are necessary to resolve the question whether vitamin D status has a preventive benefit against the development of pancreatic cancer.

4. Conclusions

Pancreatic cancer is a devastating disease with a poor five-year survival of 1–4%. Its characteristics of early spread and distant metastasis make it often diagnosed as a late stage disease and unfit for surgical treatment. Traditional chemotherapy and radiotherapy fail to show a significant benefit to the survival of PCA patients. Facing such a dilemma of dealing with advanced PCA for clinicians, developing new regimens against PCA deserves more attention. Vitamin D was originally discovered a century ago as a “vitamin” to treat rickets, and was believed to play a role only in calcium and phosphate homeostasis and bone mineralization. In the mid and late 1960s, it was realized that vitamin D3 itself was not active, and required two sequential hydroxylation steps to be activated, first in the liver to produce 25(OH)D3, the circulating form, and then in the kidneys to generate 1α,25(OH)2D3, the active form. In the late 1970s, it was found that VDR was present in many tissues and cell types not involved in calcium and bone metabolism. Later, it was demonstrated that 1α,25(OH)2D3 had anti-proliferative activity in a variety of normal and cancer cells, and anti-tumor effects in several animal models. These preclinical findings led to clinical trials using 1α,25(OH)2D3 on cancer patients. However, it was quickly found out that patients developed hypercalcemia and hypercalciuria. Consequently, several thousands of vitamin D analogs were synthesized with an attempt to eliminate/minimize these side effects, and at the same time, to enhance their anti-proliferative activity. In this respect, several analogs have been shown to be promising in vitro and in animal experiments. Unfortunately, they failed to offer promising results in early clinical trials with pancreatic cancer patients. Recently, two highly potent analogs of 1α,25(OH)2D3, namely 1α,25(OH)2D3-3-BE and MART-10, may offer promising hope to prolong the period of time-to-progression of patients with advanced pancreatic cancer, especially if the treatment is combined with docetaxel.
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