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Expanding the Role of Cadmium in Pancreatic Cancer

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COLUMN ARTICLE

Cadmium is an element commonly found in the earth's crust in low concentrations of 0.1 - 0.5 ppm (zinc is approximately 60 - 65 ppm). When purified, it is a metal with a bluish-white color with similarities to both zinc and mercury. In fact, cadmium is an impurity found in zinc ore, and it is produced as a byproduct of zinc mining and purification. Although cadmium resembles other transition metals, it is not an actual transition metal, existing primarily in the +2 oxidation state. The number of uses for cadmium has waned recently since its discovery two centuries ago. Cadmium is an anticorrosion agent, a paint additive, and a plastic stabilizer. The major consumer-related use of cadmium-containing products is the use of nickel-cadmium (NiCd) batteries [1]. In 2007, NiCd batteries contained over 80% of all cadmium in the US [1]. The amount of cadmium imported into the US was 160% of the total amount produced in the US from both primary and secondary sources [1,2]. The main routes of cadmium exposure in humans are by occupational exposure during the production of cadmium itself, purification of zinc ore, or in another chemical processes, such as plastics manufacturing [2]. In general, the production of cadmium has declined worldwide, but more so in the US. In 2006, the US production of cadmium was less than 900 metric tons, compared to nearly 20,000 metric tons of cadmium produced in China [3]. Approximately 10,000 tons of cadmium is released into the environment annually worldwide [3]. It is the persistence of cadmium, and its long biological half-life has led to its increasing health risks. Cadmium has been declared a human carcinogen by both the International Agency for Research on Cancer (IARC; 1993) and the National Toxicology Program (NTP; 2000). Over the last four decades, our understanding of cadmium as a carcinogen has increased beginning with the first report linking occupational exposure to cadmium and prostate cancer [4]. These findings are supported by more recent reports linking cadmium exposure and prostate cancer [5]. Also, cadmium has been, at least loosely, implicated in the development of multiple other cancers such as lung, kidney, bladder, pancreas and breast cancers [3,6,7].

The primary focus of this column is the expanding role of cadmium in the development of pancreatic cancer. Information from the American Cancer Society suggests that pancreatic cancer isn't the most common cancer with only 53,000+ new diagnoses in 2017; yet, there were also 43,000+ deaths directly due to pancreatic cancer [8]. The lifetime risk for pancreatic cancer is only 1.5%, which makes it the twelfth most prevalent of all cancers, but the estimated death rate puts pancreatic cancer as the fifth most lethal of all cancers between 2010 - 2014, and the third most deadly in 2017 [8]. This alarming trend suggests that as the prevalence of pancreatic cancer has risen slowly over the last decade, the death rate has remained alarmingly high. The high mortality rate would signal the need for significantly more research as to the underlying causes of pancreatic cancer and the improvement of treatment. Risk factors for developing pancreatic cancer include

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tobacco use/smoking, obesity, chemical exposures (both occupational and environmental). Cadmium exposure as a by-product of smoking and chemical exposure has become increasingly relevant. As discussed earlier, there have been an increasing number of reports that have linked or attempted to link, exposure to cadmium and the development of various cancers [3-7]. In a chapter by Hartwig [9], the author describes in excellent detail the potential actions of cadmium on intracellular systems which may lead to the development of cancer. The generation of reactive oxygen species (ROS) or free radicals appears to have some impact, but it is the reported effects associated with cadmium on apoptotic pathways that is particularly intriguing. Cadmium reportedly interacts with zinc-binding sites interfering with DNA repair proteins (XPA, PARP-1, and p53 in particular) [9]. Changes in protein function will alter the cellular ability to repair during apoptosis leading to uncontrolled growth and mutations. The ability of cadmium as a divalent cation to interact with the zinc-binding sites as well as thiol groups on proteins is well understood [9]. Now there must be attempts to link exposure to cadmium and the development of pancreatic cancer. Concentrations of cadmium were reported to be five-times higher in pancreatic tumor tissue compared to control pancreas tissue. Tissue concentrations of cadmium surrounding tumors were still significantly greater than cadmium values in control tissue [10]. Additional work is needed to strengthen this link between cadmium and pancreatic cancer. An early study suggested that there is, in fact, a link between cadmium exposure and the development of pancreatic cancer via cadmium-mediated activation of various oncogenes [11]. In a recent observational study, Chen., *et al.* [12] reported that there was a gender-specific variation in cadmium-related effects. In men, a significant cadmium exposure - cancer risk ratio was reported, but this effect was not observed in females, suggesting gender-bias in the development of pancreatic cancer due to cadmium exposure. This effect was not observed in other reports and the recent American Cancer Society information also suggests that there is a near equal distribution of pancreatic cancer cases in men and women [8]. Attempts to link cadmium exposure in various occupations and pancreatic cancer has suggested and strengthened the hypothesis that cadmium exposure is a major factor in the development of pancreatic cancer [13,14]. Kriegel., *et al.* [13] reported that the odds-ratio for pancreatic cancer risk was significantly related to serum cadmium concentration as well as farming status. The presence of cadmium in various agriculture chemicals would have led to the farming exposure to cadmium. This report was an early statement about the occupational and environmental exposure to cadmium. Luckett., *et al*. [14] furthered this hypothesis by demonstrating a significant odds-ration between urinary cadmium concentration and the incidence of pancreatic cancer. The authors then showed that elevated urinary cadmium is significantly linked to high levels of smoking, occupational exposure to certain paints, working in shipyards and consumption of grain contaminated with cadmium. Collectively, there is an expanding body of evidence which suggests that cadmium is a risk factor for the development of pancreatic cancer. As our understanding of the cellular changes associated with cadmium exposure and pancreatic cancer improve, the development of specific therapies targeting these cadmium-mediated effects should aid in reducing the mortality rate associated with pancreatic cancer.

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