Hypothesis

Is Cadmium a Cause of Human Pancreatic Cancer?¹

Gary G. Schwartz² and Isildinha M. Reis

Abstract

Little is known about the etiology of pancreatic cancer, which is an important cause of cancer mortality in developed countries. We hypothesize that exposure to cadmium is a cause of pancreatic cancer. Cadmium is a nonessential metal that is known to accumulate in the human pancreas. The major risk factors for pancreatic cancer (increasing age, cigarette smoking, residence in Louisiana, and occupations involving exposure to metalworking and pesticides) are all associated with increased exposure to cadmium. Our meta-analysis of cohorts with high exposure to cadmium is also consistent with an increased risk of pancreatic cancer (standardized mortality ratio = 166; 95% confidence interval, 98–280; \( P = 0.059 \)). Cadmium can cause the transdifferentiation of pancreatic cells, increases in the synthesis of pancreatic DNA, and increases in oncogene activation. Thus, cadmium is a plausible pancreatic carcinogen. The cadmium hypothesis provides a coherent explanation for much of the descriptive epidemiology of pancreatic cancer and suggests new avenues for analytical research.

Introduction

Cancer of the pancreas is an important cause of cancer mortality in developed countries and accounts for more than 28,000 deaths in the United States per year. Pancreatic cancer produces few specific symptoms in its early stages and is usually detected at an advanced and incurable stage. This contributes to pancreatic cancer having the worst survival of any major cancer; the average survival after diagnosis is less than 6 months, and fewer than 5% of patients survive 5 years (1, 2).

The etiology of pancreatic cancer is obscure (see Refs. 3–5 for reviews of the epidemiology). Incidence rates for pancreatic cancer increase exponentially with age beginning at about age 40 years, are approximately 50% higher among males than females, and are higher among blacks than whites. Despite considerable epidemiological study, the only modifiable risk factor that has been established is cigarette smoking. However, the identity of the carcinogen(s) in cigarette smoke is unknown. Few strong occupational risks have been detected, although moderate risks have been associated with several industries, including metalworking occupations and pesticide exposure (6). Mapping of United States mortality rates from pancreatic cancer has identified significantly elevated rates in southern Louisiana (7), but the cause of that cluster remains largely unexplained.

We hypothesize that exposure to cadmium is a cause of pancreatic cancer. The purposes of this study are to: (a) describe the cadmium hypothesis for pancreatic cancer; (b) test the hypothesis using available epidemiological data; (c) review evidence indicating that cadmium is a plausible pancreatic carcinogen; and (d) propose new areas for analytic investigation. Before describing the cadmium hypothesis, we review some toxicological properties of cadmium.

Toxicological Properties of Cadmium

Cadmium, atomic number 48, is a soft, silver-white metal that is found naturally at low levels in rocks and soil. Cadmium is used in a variety of industries, e.g., in nickel-cadmium batteries and electroplating, as a component in metallurgical and brazing-soldering alloys, in pigments, and as a stabilizer for plastic. Most of the cadmium produced in the United States is extracted during the smelting of other metals, such as zinc, lead, or copper. Smelters are a major source of airborne cadmium contamination. Other sources of environmental cadmium are the burning of fossil fuels and waste materials and the use of phosphate fertilizers and sewage sludge (8–11).

Cadmium that is present in soil as the result of industrial emissions or fertilization can be taken up selectively by edible plants, producing cadmium concentrations many times that of the surrounding soil (12). Similarly, many water plants biomagnify the levels of cadmium in the surrounding water. Cadmium levels in fish, especially Mollusca and Crustacea (e.g., oysters, shrimp, crab, and crayfish), can be greatly elevated (13). Most of the cadmium in crustaceans is contained within a single organ, the hepatopancreas (14–16), which is commonly consumed by humans. For example, plants grown for 7 days in 0.00224 ppb cadmium were fed to Louisiana red swamp crayfish (Procambarus clarkii) for 14 days. Accumulation of cadmium in hepatopancreata increased from 176.8 ppb on day 0 to 4657.6 ppb on day 14 (17). Cadmium levels in edible crab (Cancer pagurus) may be as high as 30–50 parts/million (18). Consumption of one crab meal per week has been estimated to exceed the WHO provisionally tolerable cadmium intake of less than 500 μg (19, 20).

Food is the main source of cadmium for the non-smoking population. Estimates of dietary cadmium intake worldwide range from 10–40 μg/day in nonpolluted areas to several hundred micrograms in cadmium-polluted regions. In the United States, the average person consumes approximately 30 μg of cadmium per day in food and absorbs 1–3 μg from the gastrointestinal tract. Smoking is an important source of cadmium exposure (21). One cigarette contains approximately 1–2

¹This paper is dedicated to Dr. Barbara S. Hulka on the occasion of her retirement.

²To whom requests for reprints should be addressed, at Comprehensive Cancer Center of Wake Forest University, Winston-Salem, North Carolina 27157; (G. G. S.), and Division of Biostatistics, Sylvester Comprehensive Cancer Center, University of Miami, Miami, Florida 33101 [I. M. R.]

Received 8/5/99; revised 10/1/99; accepted 10/13/99.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
µg of cadmium, and smokers absorb an additional 1–3 µg cadmium/day from the respiratory tract.³

Most of the cadmium in the body is bound to metallothioneins, low molecular weight proteins that function in the homeostasis of essential metals, e.g., zinc (22, 23). The cadmium-metallothionein complex is distributed to various tissues and organs and is ultimately reabsorbed in kidney tubuli (24). Because the body has no mechanism for the excretion of cadmium, cadmium accumulates in tissues. The half-life of cadmium in kidney cortex is 10–30 years. In humans, the largest amount of cadmium is deposited in the kidneys and liver, followed by the pancreas and lungs.

In 1993, the IARC classified cadmium and cadmium compounds as known human carcinogens (i.e., category 1 compounds; Ref. 25). The most convincing human data implicate cadmium as a carcinogen in the lung, with equivocal evidence at other sites [e.g., prostate (26) and kidney (27)]. To our knowledge, this is the first report to propose that cadmium is a cause of human pancreatic cancer.

The Cadmium Hypothesis for Pancreatic Cancer

We suggest that many of the known risk factors for pancreatic cancer are intelligible in terms of increased exposure to cadmium. For example, the increasing incidence rate of pancreatic cancer with age is intelligible because cadmium levels are undetectable in the pancreata of newborns and accumulate with age, reaching their peak at about age 50 years (28).

The increased risk associated with smoking also is understandable and is consistent with the cadmium content of cigarettes. The mean cadmium content in the fat of smokers is four times that of nonsmokers (29). Autopsy studies consistently demonstrate that the pancreata of smokers contain approximately twice the amount of cadmium as the pancreata of age-matched nonsmokers (30, 31).

The significantly elevated rates for pancreatic cancer in Louisiana also are intelligible. Industrial activity in Louisiana has contaminated much of the wetlands with cadmium (32). For example, sampling of indoor and outdoor air in 53 households in Louisiana revealed that 64 of 315 samples (20.3%) exceeded the Environmental Protection Agency’s guidelines for cadmium (32). For example, cadmium is a significant contaminant of both pesticides and pigments. Similarly, many metal workers are exposed to cadmium and cadmium fume, e.g., via welding or soldering (55, 56). Solderers are known to have significantly elevated levels of cadmium in serum (57) and to have a significantly increased risk of pancreatic cancer (58). These risk factors are summarized in Table 1.

Tests of the Cadmium Hypothesis

In 1977, Schrauzer et al. (59) correlated data on dietary consumption of various trace elements per capita in 29 countries with the corresponding age-adjusted mortality rates from various cancers. They noted significant positive correlations between the estimated dietary intake of cadmium and pancreatic cancer mortality in both men and women (r = 0.48 and 0.25 for men and women, respectively). Thus, their ecological study provides tentative support for the hypothesis that exposure to cadmium increases the risk of pancreatic cancer.³ However, the question of greatest interest, i.e., whether individuals with high exposure are at increased risk, cannot be answered by ecological data. Therefore, we asked, “Are individuals with high exposures to cadmium at increased risk of pancreatic cancer?”.

Methods

We searched MEDLINE from January 1966 through March 1999, in all languages, for reports of the mortality of cadmium-exposed workers. Studies cited in these reports were also reviewed. Twenty-five studies were obtained. The majority of these studies concerned the association between cadmium and cancers of the lung and/or prostate. None of the studies were designed to investigate the association of cadmium exposure and cancer of the pancreas. However, five of these studies provided numerical data on observed and expected deaths from pancreatic cancer. Because the number of pancreatic cancer deaths in each of the studies was small, we combined the data

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Explanation by cadmium hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Cadmium accumulates in the pancreas with age.</td>
</tr>
<tr>
<td>Smoking</td>
<td>Cadmium is a contaminant of cigarettes. The pancreata of smokers contain twice the amount of cadmium as the pancreata of nonsmokers.</td>
</tr>
<tr>
<td>Geography</td>
<td>Increased rates in Louisiana are consistent with cadmium pollution. International mortality rates are positively correlated with dietary cadmium.</td>
</tr>
<tr>
<td>Occupation</td>
<td>Occupations with high exposure to cadmium show increased mortality from pancreatic cancer.</td>
</tr>
</tbody>
</table>

³ There is no evidence that Schrauzer et al. (59) were aware of the present hypothesis. Their ecological study, published 22 years earlier, concerned the possible confounding influence of trace elements (e.g., cadmium) on the anticancer properties of selenium.

³ For example, cadmium is a significant contaminant of both pesticides and pigments. Similarly, many metal workers are exposed to cadmium and cadmium fume, e.g., via welding or soldering (55, 56). Solderers are known to have significantly elevated levels of cadmium in serum (57) and to have a significantly increased risk of pancreatic cancer (58). In 1977, Schrauzer et al. (59) correlated data on dietary consumption of various trace elements per capita in 29 countries with the corresponding age-adjusted mortality rates from various cancers. They noted significant positive correlations between the estimated dietary intake of cadmium and pancreatic cancer mortality in both men and women (r = 0.48 and 0.25 for men and women, respectively). Thus, their ecological study provides tentative support for the hypothesis that exposure to cadmium increases the risk of pancreatic cancer. However, the question of greatest interest, i.e., whether individuals with high exposure are at increased risk, cannot be answered by ecological data. Therefore, we asked, “Are individuals with high exposures to cadmium at increased risk of pancreatic cancer?”.

³ There is no evidence that Schrauzer et al. (59) were aware of the present hypothesis. Their ecological study, published 22 years earlier, concerned the possible confounding influence of trace elements (e.g., cadmium) on the anticancer properties of selenium.
in a meta-analysis to obtain a more precise estimate of the risk associated with cadmium exposure. We restricted our meta-analysis to the most recent report on each cohort. After removing duplicate data (updates on cohorts that were reported previously), data were available for four cohorts (60–62). We estimated a summary SMR (3/100) and 95% CI for pancreatic cancer after testing for homogeneity of the study-specific SMRs. The summary estimate was computed under a fixed effects model (63, 64).

All of the studies involved cohorts of males; Järup et al. (62) also reported data for females. To determine whether the data on females affected the summary SMR, we performed two meta-analyses, one comprised of male workers, and another comprised of male workers with data on females included as a separate cohort.

Results

Table 2 presents characteristics of the available studies. There is no evidence of heterogeneity of the study-specific SMRs for males (P = 0.762). The estimated summary SMR for males is 162 (95% CI, 94–279), P = 0.082 for the test of a significant difference from SMR = 100. The SMR of 220 for females did not differ significantly from the summary SMR for males (summary SMR = 162; P = 0.766). The test of heterogeneity for the SMRs for the four study cohorts (men and women) is also not significant (P = 0.889). Therefore, we calculated a summary estimate combining the data from males and females. The overall summary SMR is 166 (95% CI, 98–280; P = 0.059).

The graphical presentation of the SMRs and the corresponding 95% CIs illustrate the gain in precision obtained from the meta-analysis. Although the total number of deaths is modest, the consistency of the data in the four cohorts, the elevated risks in males and females, and the findings of our meta-analyses support the hypothesis that exposure to cadmium increases the risk of death from pancreatic cancer.

It is possible that these results reflect the confounding effects of smoking. Although data on smoking histories generally were not available, the percentage of smokers among the Swedish cadmium workers was similar to that of the general Swedish population in the 1980s (65). It is unlikely that the excess of pancreatic cancer among the British cadmium workers was the result of confounding by smoking because these workers did not experience an excess of lung cancer (18 cases observed versus 17.84 expected cases). Conversely, because these cohorts experienced significantly increased mortality from competing causes (e.g., nephritis and nephrosis and accidental poisoning by heavy metals and their fumes (ICD-8 E866)), the observed risk for pancreatic cancer may underestimate the true risk.

Biological Plausibility of the Cadmium Hypothesis

Our meta-analysis suggests that individuals with increased exposure to cadmium have an increased risk of pancreatic cancer. We next asked, “Is cadmium a plausible carcinogen in the pancreas?” In animals, both carcinogenic and anticarcinogenic effects of cadmium have been described previously (66). However, the majority of evidence indicates that cadmium is indeed carcinogenic in the pancreas. Possible mechanisms for the carcinogenicity of cadmium include substitution of cadmium for zinc, transdifferentiation, and oncogene activation, described below.

The substitution of cadmium for zinc may be a central mechanism underlying the carcinogenicity of cadmium. Zinc is an essential trace element that is required for the synthesis of DNA, RNA, and protein and thus for cell division (67). The pancreas contains high levels of zinc. Conversely, cadmium is a toxic element for which there is no known human require-

---

Table 2  
Review and meta-analysis of risk of death from pancreatic cancer in cohorts exposed to cadmium

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Cohort size</th>
<th>Follow-up period</th>
<th>Deaths (Obs, Exp)</th>
<th>SMR</th>
<th>95% CI</th>
<th>SMR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Elinder et al (60)</td>
<td>male cadmium-nickel battery workers, Oskarshamn, Sweden</td>
<td>522</td>
<td>1951-83</td>
<td>3, 2.3</td>
<td>130</td>
<td>27 - 380</td>
<td></td>
</tr>
<tr>
<td>2. Sorahan et al (61)</td>
<td>male copper cadmium alloy workers, England and Wales</td>
<td>347</td>
<td>1946-92</td>
<td>4, 1.8</td>
<td>218</td>
<td>59 - 558</td>
<td></td>
</tr>
<tr>
<td>3. Järup et al (62)</td>
<td>battery workers, Kalmar, Sweden</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>females</td>
<td>183</td>
<td>1951-92</td>
<td>1, 0.4</td>
<td>220</td>
<td>6 - 1228</td>
<td></td>
</tr>
</tbody>
</table>

Meta-analysis

<table>
<thead>
<tr>
<th>Test of homogeneity of the SMRs</th>
<th>Summary SMR and 95% CI</th>
<th>Test of summary SMR = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>p = 0.762</td>
<td>162 94 - 279</td>
<td>p = 0.082 162</td>
</tr>
<tr>
<td>p = 0.889</td>
<td>166 98 - 280</td>
<td>p = 0.059 166</td>
</tr>
</tbody>
</table>

*Exact confidence limits.

---

6 The abbreviations used are: SMR, standardized mortality ratio; CI, confidence interval.
Hypothesis: Cadmium and Human Pancreatic Cancer

Cadmium is one of the most potent agents known to induce transdifferentiation of the pancreas (72). Transdifferentiation, or metaplasia, is a change from one differentiated cell type to another, e.g., from a mature pancreatic cell to a mature liver cell (hepatocyte; Ref. 73, 74). Repeated injections of cadmium induced hepatocytic foci in the pancreata of more than 93% of rats (75). Because the process of metaplasia involves cellular dedifferentiation, proliferation, and ultimately redifferentiation (76), agents that induce metaplasia (i.e., cadmium) may place cells at increased risk for neoplasia (77, 78).

As noted above, cadmium is mitogenic to pancreatic cells (79). For example, relative to mice injected with saline, mice injected with 4 mg/kg cadmium chloride had a 2.5-fold increase in the incorporation of [3H]thymidine in the pancreas. The increased DNA synthesis is thought to reflect the increased synthesis of metallothionein (80, 81). Injecting rats with 4 and 8 mg/kg cadmium caused a 9.8- and 17.9-fold increase in pancreatic metallothionein (82). Cadmium is also carcinogenic in the pancreas. For example, injecting Wistar rats with cadmium chloride caused a significant increase in the incidence of pancreatic islet cell tumors (8.5% versus 2.2%; Ref. 83). In addition to its direct effects on pancreatic cells, cadmium may influence carcinogenesis indirectly, e.g., by inducing specific genes such as metallothionein, or by acting as a toxin and thereby disrupting cellular function (84). For example, the cadmium-metallothionein can cause DNA strand breaks (85). Moreover, transgenic mice that overexpress metallothionein (metallothionein III) develop a selective and progressive degeneration of pancreatic acinar cells (86). It is intriguing in this regard that increased expression of metallothionein, as measured by immunohistochemistry, has been associated with metastasis, poor prognosis, and poor histological grade in human pancreatic cancers (87).

Cadmium can induce or regulate the activation of several oncogenic proteins and tumor suppressor proteins that are known to be overexpressed in human pancreatic cancers, e.g., ras proteins and the p53 protein (88–90). In order for ras proteins to become oncogenic, a farnesyl group must be added. The enzyme normally responsible for this reaction, farnesyl:protein transferase, is a zinc metalloenzyme. Cadmium can substitute for zinc in this reaction and can farnesylate some H-ras motifs that are normally not affected by zinc (91). Cadmium also induces expression of the c-fos oncogene (92), which is increased in many pancreatic cancers and inhibits the function of the p53 tumor suppressor protein (93, 94). Finally, cadmium can enhance the initiation of carcinogenesis induced by other carcinogens, such as dimethylnitrosamine and hepatitis B, and inhibits DNA repair (95–98).

In summary, cadmium can cause the transdifferentiation of pancreatic cells, increase the synthesis of pancreatic DNA, and regulate the expression of oncogenes that are implicated in pancreatic carcinogenesis. Thus, cadmium is a plausible pancreatic carcinogen. The cadmium hypothesis for pancreatic cancer is summarized schematically in Fig. 1.

### Opportunities for Future Study

The cadmium hypothesis suggests novel opportunities for molecular epidemiology. For example, because blood, urine, and several organs (e.g., liver, kidney, and pancreas) act as dosimeters for cadmium, samples of these materials could be used for case-control studies. The cadmium hypothesis predicts that, controlling for age and smoking history, cadmium levels should be higher in biological samples from persons with pancreatic cancer than in corresponding samples from persons without pancreatic cancer. Such studies would be free from many of the biases that affect interview-based case-control studies, e.g., recall bias. The hypothesis also makes predictions for genetic epidemiology. For example, because metallothioneins play a role in the detoxification of cadmium, the association between cadmium and pancreatic cancer may be modified by variation in the genes that encode metallothioneins (105, 106).

Molecular epidemiological studies of cadmium exposure are practicable. Cadmium can be measured in blood, urine, and tissues by atomic absorption spectrophotometry and can be measured in vivo by neutron activation analysis or X-ray fluorescence (107, 108). The relative merits of sampling urine and blood for measuring exposure to cadmium have recently been discussed (109, 110). In general, blood cadmium reflects both cumulative body burden and recent exposure. Urinary cadmium reflects the cumulative body burden of cadmium long after exposures have ceased, but it may be inaccurate if renal tubular damage has occurred.

The cadmium hypothesis has implications for cancer prevention. For example, if the increased risk of pancreatic cancer associated with smoking is due, at least in part, to the cadmium content of cigarettes (111), then passive exposure to cigarette
smoke may increase the risk for pancreatic cancer. This is because side stream smoke contains approximately 50% of the cadmium in mainstream smoke (112). Compared to nonsmokers not exposed to cigarette smoke, the cadmium content of the blood of nonsmokers exposed to cigarette smoke from active smokers is significantly elevated (113). It is noteworthy that an increased risk of pancreatic cancer from exposure to passive smoking was recently reported in a case-control study (114). These findings suggest that the attributable risk for cigarettes as a cause of pancreatic cancer may be greater than is presently recognized. Lastly, the cadmium hypothesis has implications for the cigarette industry because it suggests that the risk of pancreatic cancer due to smoking could be reduced by tobacco that is produced in the absence of cadmium-containing fertilizers and sludges (115, 116).

In conclusion, the cadmium hypothesis provides a coherent and biologically plausible explanation for much of the descriptive epidemiology of pancreatic cancer and suggests new avenues for analytic research. Because pancreatic cancer has a grim prognosis and there are few means for its prevention, efforts to confirm or refute this hypothesis should be vigorously pursued.

Acknowledgments
We thank Jim Schleselman for helpful advice on meta-analysis, Violet Lagari for bibliographic assistance, and the anonymous reviewers for their valuable comments.

References
Hypothesis: Cadmium and Human Pancreatic Cancer


Is Cadmium a Cause of Human Pancreatic Cancer?

Gary G. Schwartz and Isildinha M. Reis


Updated version
Access the most recent version of this article at:
http://cebp.aacrjournals.org/content/9/2/139

Cited articles
This article cites 97 articles, 10 of which you can access for free at:
http://cebp.aacrjournals.org/content/9/2/139.full#ref-list-1

Citing articles
This article has been cited by 8 HighWire-hosted articles. Access the articles at:
http://cebp.aacrjournals.org/content/9/2/139.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.