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REVIEW

The relationship between oral cancer and cadmium: a review

Samed Satir[1]

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Abstract
Cadmium (Cd) has been classified as a type I carcinogen. Since it is ingested orally through food and tobacco use, Cd is likely to be closely related to oral cancers. The relationship between cadmium and oral cancer was investigated using papers on Pubmed and Web of Science. Thus a total of 11 studies from these databases were included in the review. Cd concentrations were significantly higher in both the blood and hair of oral cancer patients than in controls. Additionally, it has been reported that Cd increases the activity of reactive oxygen species. Tobacco plants contain varying levels of Cd. The presence of high Cd concentrations in patients who use tobacco products and develop oral cancer is strong evidence that Cd is directly related to oral cancer. While planning a study to determine the Cd concentrations in biological samples, it is advisable to examine the methodologies of previous studies and to avoid technical deficiencies. New cell line studies are required to explain the relationship between Cd and autophagy-apoptosis.

Keywords Cadmium · Oral cancer · Oral squamous cell carcinoma · Autophagy

Introduction

Cadmium (Cd) is a toxic heavy metal that has accumulated in our environment as a result of mining and industrial activity [1]. Humans are exposed to Cd due to food, water, soil/waste, air and tobacco products [2–5]. Cd binds to metallothionein (MT), an organic molecule, and competes for MT in organisms with essential trace elements such as zinc (Zn) for MT in organism [6, 7]. Cd is primarily stored in the liver, kidney and bones [1, 8]. It is well established that Cd plays a role in the aetiology of a variety of diseases, including anaemia and osteoporosis [9]. Many biological materials have been used to demonstrate its accumulation in the human body, including blood, hair, saliva, breast milk, and teeth [10–12]. In addition, numerous many animal experiments have been conducted to demonstrate the effects of Cd on living tissues [13–15].

The International Agency for Research on Cancer has classified Cd as a type I carcinogen [16]. Cd has been linked to prostate, pancreatic, breast, lung, and bladder cancer [17–19]. Cd's potential carcinogenicity has also been highlighted in animal experiments and cell line studies [20, 21].

One of the most significant sources of Cd is tobacco [22, 23]. Cd is likely to be closely related to oral cancers because it is ingested through food and the use of tobacco products. The aim of this study is to review published research on the relationship between cadmium, a toxic and carcinogenic trace element, and oral cancer.

Methods

Search strategy

Between 1st and 5th May 2021, a systematic review of the literature on the relationship between cadmium and oral cancer in Pubmed and Web of Science Library was conducted. The search was performed by using the keywords “cadmium oral cancer” or “cadmium mouth cancer” or “cadmium dental” or “cadmium saliva” or “cadmium oral mucosa”.

Study selection

The study excluded reviews, case reports, letters to the editor, and articles that were not open access, were not written in English, or contained the term Cd only in their references.

✉ Samed Satir
samed.satir@alanya.edu.tr

[1] Faculty of Dentistry, Oral and Maxillofacial Radiology, Alanya Alaaddin Keykubat University, Konaklı, Mustafa Kemal Boulevard, Alanya, 07490 Antalya, Turkey

Results

Literature search and study characteristics

A total of 11 studies were included in the systematic review (Fig. 1). The 11 articles were comprised of 7 case–control studies, a cross-sectional study, and 3 cell lines researches with oral squamous cell carcinoma (OSCC) cells. The main characteristics of the studies are summarized in Table 1. The numerical data obtained from the case–control studies are shown in Table 2.

Cd concentration in biological samples of oral cancer patients

Cd concentrations in oral cancer patients' blood and hair were consistently higher than controls in all case–control studies except one [24–27, 31, 32, 34]. Cd was not detected in any of the remaining study's samples, including those from control patients [31]. In a study in which Cd was detected in calculus, the study group's Cd concentration was found to be higher than the control group's [32]. Three studies established control and case groups based on whether or not individuals had cancer [25–27]. In the other three studies, tobacco product usage was considered when forming the groups [24, 31, 32]. In the only remaining study, the relationship between teenagers and the garbage disposal profession determined the separation of control and case groups [34]. According to a study of various cancer types in different parts of the body, all oral cancer patients who chewed tobacco had significantly higher Cd concentrations in their hair than control subjects [26].

Effect of Cd on apoptosis and autophagy

Cd has been shown to increase the activity of reactive oxygen species (ROS) in studies using OSCC cell lines [28, 30, 33]. Autophagy and apoptosis have been shown to reduce oxidative stress in OSCC cells, but they can also result in the death of these cells [28, 30, 33].

Technique used to determine Cd concentration

Atomic absorption spectroscopy (AAS) was used in almost all of the studies we included in the review to determine the Cd concentration [24–27, 31, 34]. The only study that used inductively coupled plasma-mass spectroscopy (ICP-MS) also the only one that examined Cd concentration in calculus [32]. All studies that measured Cd concentration in hair samples used certified reference samples. In half of the studies in which blood samples were used, detection limits were not provided [24, 34]. It was observed that the detection limits of the study in which no Cd was detected in any sample were significantly lower than the scanning limits presented of the other study [31] (Table 2).

Discussion

In some of the case–control studies included in this review, the groups were selected according to their tobacco product use, and the amount of Cd in tobacco users' biological materials was generally found to be high. In addition, other researchers which question individuals' use of tobacco products demonstrates that authors focus on the relationship between OSCC and Cd exposure from tobacco products. According to the European Food Safety Authority (EFSA) and the World Health Organization (WHO) recommend a weekly Cd intake limit of 2.5 µg/kg and 5.8 µg/kg respectively [35, 36]. Smokers are estimated to consume twice the amount of Cd daily as non-smokers [37, 38]. Some studies report that approximately 10% of the Cd in tobacco products accumulates in the lungs and 20–50% enters the circulation system [27, 39, 40]. Additionally, some studies indicate that not only tobacco is a source of Cd exposure, but also various seafood and vegetables [5, 41]. While tobacco products are not the only source of Cd exposure for smokers, they are widely accepted as the primary etiological cause of Cd-induced toxic and carcinogenic effects, with the exception of occupational exposure [42].

Smoking can damage the oral epithelium and cause OSCC [28]. Numerous OSCC cell line studies conducted to clarify the mechanism of neoplasm development in the oral mucosa, have revealed that Cd increased ROS, which is thought to activate the tumorigenesis signal [30, 33]. According to all three studies, autophagy and apoptosis are bidirectional and may result in the death of the cell while performing their protective function. That is, it is believed that autophagy and apoptosis play a critical role in the diagnosis, prevention and treatment of OSCC. So et al. demonstrated that Pin1, one of the molecules they examined, remained unaffected by Cd-induced autophagy. They stated that while autophagy protects the cell from Cd, it is also associated with poor prognosis [28]. Another cell line study using the heme oxygenase-1 (OH^-) antioxidant enzyme revealed a positive correlation between the increase in Cd-induced ROS and the increase in OH^-. The level of OH^- induction has been predicted to be a useful tool for determining the extent of oxidative stress in cells. However, it has been reported that high levels of OH^- may exacerbate cellular stress, thereby worsening rather than resolving the condition [30]. Autophagy has also been linked to metastasis and invasion. Additionally, autophagy causes cell death and tumorigenesis. While cell line studies have reported that

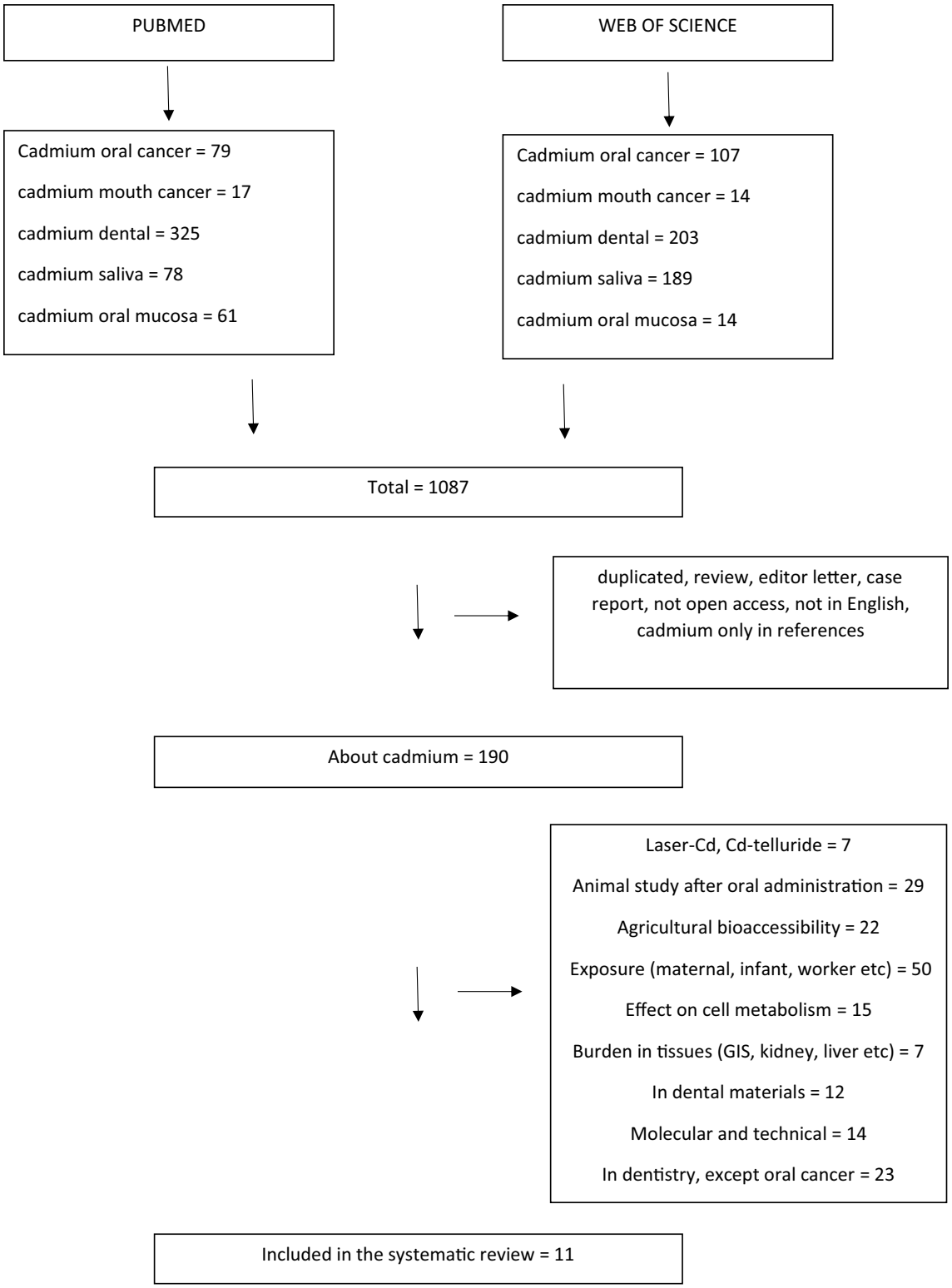

Fig. 1 Flow chart of selected articles

identical enzymes behave differently in different cell types and yield inconsistent results, it has also been noted that little is known about the effect of Cd exposure on OSCC [33]. In addition, all three studies mentioned the close relationship between tobacco product usage and OSCC [28, 30, 33]. Thus, while the effect of Cd, which is present in high

Table 1 Study characteristics

	Type	Data collection and scope	Samples/groups (n)	Results	Oral cancer in discussion
Kazi et al. [24]	Case–control	Oral cancer patients Blood and hair Cd, Zn	Study (96) Control (110)	High Cd in blood and hair in the study group	Exposure to Cd oxide fumes through tobacco smoking or chewing increases the risk of death from oral cancer
Arain et al. [25]	Case–control	Oral cancer patients Blood and hair Cd	Study (1449) Control (1155)	High Cd in blood and hair in the study group	Cd affects the natural cell cycle as well as apoptotic pathways. But the role of Cd in the development of different types of oral cancer is not yet clear
Wadhwa et al. [26]	Case–control	Cancer patients Hair Cd, Ni, As, Se, Zn	Study (125) Control (94)	High Cd in hair in the study group	Cd, which is the antagonist of Zn, may bind to the site of Zn in DNA and cause toxicity and cancer
Kazi et al. [27]	Case–control	Cancer patients Hair Cd, Ni, As, Se, Zn	Study (159) Control (105)	High Cd in hair in the study group	Poor oral hygiene and unsuitable dentures with tobacco and alcohol consumption may increase the risk of oral cancer
So et al. [28]	Cell lines	Pin1 GSK3αβ	YD8 OSCC cell	Induced by p-Ser-GSK3αβ autophagy protects cells against Cd-induced apoptosis	Suppression of autophagy in OSCC cells resulted in increased apoptosis in response to Cd. But molecular mechanisms leading to autophagy in OSCC is uncertain
Fillman et al. [29]	Cross-sectional	Adolescents Urine Cd, As Salivary telomere length	(351)	Telomere length decreased as urinary Cd increased	The fact that cadmium causes DNA damage and oxidative stress may help explain its mutagenic effects
So et al. [30]	Cell lines	HO^- MAPK/JNK1	YD8 and YD10B OSCC cell	Cd is an important cause of ROS and influences the apoptotic mechanism	Cd-induced oxidative stress is induced by catalase disorders, and oral cancer cells can respond to oxidative stress through autophagy-apoptosis and induction of HO^-
Bandeira et al. [31]	Case–control	Cancer patients Blood Cd, Pb, Cu, Mn, As, Cr	Study (76) Control (15)	Cd not detected in any sample	The relationship between heavy metals and oral cancers is controversial
Zhang et al. [32]	Case–control	Oral cancer patients Dental calculus Cd	Study (85) Control (67)	High Cd in dental calculus in the study group	Long-term chronic exposure to Cd by betel quid chewing and smoking causes changes in oral mucosal epithelial cells and leads to conversion to oral cancer
Fan et al. [33]	Cell lines	NUPR1	CAL27 OSCC cell	Interaction between chronic Cd exposure and ROS-NUPR1 signaling	Repeated Cd exposure activates autophagic pathway and may induce OSCC cell invasion and migration
Alabi et al. [34]	Case–control	Adolescent e-waste scavengers Blood Cd, Pb, Ni, Cr DNA damage in mucosa	Study (95) Control (104)	High Cd in blood and DNA damage in the study group	DNA damage detected in buccal mucosal epithelial cells may be evidence for the association of heavy metal exposure with epithelial carcinogenicity

Table 2 Studies aimed to determine the Cd concentration in biological samples

	Region	Results (min–max)			Technic	Detection limits	
		Hair	Blood	Dental calculus		Hair	Blood
Kazi et al. [24]	Pakistan	1.21–7.64 µg/g	3.95–9.87 µg/L		AAS	Use of certified hair samples (BCR 397)	
Arain et al. [25]	Pakistan	1.35–7.12 µg/g	2.65–16.8 µg/L		AAS	Use of certified hair samples (CRM 397), 97.8–98.9%	LOD 0.28 µg/L LOQ 0.81 µg/L
Wadhwa et al. [26]	Pakistan	0.85–7.53 µg/g			AAS	Use of certified hair samples (CRM 397), 96.4–99.3%	
Kazi et al. [27]	Pakistan	1.06–7.34 µg/g			AAS	Use of certified hair samples (CRM 397), 96.4–99.3%	
Bandeira et al. [31]	Brazil		NA		AAS		LOD 0.01 µg/mL LOQ 0.1 µg/mL
Zhang et al. [32]	China			99–700 ng/g	ICP-MS		
Alabi et al. [34]	Nigeria		0.38–12.35 µg/L		AAS		

AAS atomic absorption spectroscopy, *ICP-MS* inductively coupled plasma mass spectroscopy, *LOD* limit of detection, *LOQ* limit of quantification

concentrations in tobacco products, at the cellular level is unknown, it is known to cause oxidative stress.

The numerical data for the Cd concentration in calculus are expressed in ng/g units, which can easily be converted to the microgram/g unit used in all studies on Cd concentration in hair [32]. The authors compared their Cd concentration they obtained in calculus to the results of a similar study and stated that it was consistent with the literature [43]. The findings of this study indicate that the Cd content of calculus is lower than that of hair. This could be because Cd accumulates in different tissues at different concentrations or because the concentration determination technique used is different.

Presently, ICP-MS is preferred over AAS for Cd analysis because it is faster and more sensitive [44]. In Bandeira et al.'s study, in which AAS was used, Cd was not detected in any sample. Cd concentrations below detection limits have been associated with smoking cessation in cancer patients [31]. However, when the detection limits of this study are compared to those of similar studies, it is clear that a very low detection limit was determined. The inability to detect Cd in this study could be due to a failure to establish an appropriate detection limit or a technical issue with the device used. In a study where Cd concentrations was determined using calculus, it was emphasized that before using the ICP-MS to determine the concentration, the appropriate method should be established and the detection limits correctly determined [43].

In one study, DNA damage was examined in exfoliated buccal mucosa cells, and it was found to be significantly higher in young e-waste scavengers than in the control group [34]. In an editorial letter published in the same year for this study, it was reported that demonstrating DNA damage with samples obtained from exfoliated buccal mucosa cells may not be reliable [45]. In the same editorial letter, referring to a study that found no difference in the cell nuclei of smokers and non-smokers, it was claimed that the method used by Alabi et al. made it impossible to demonstrate that heavy metals cause oral cancer. Fillman et al. stated that Cd exposure alters the telomere length in saliva and induces oxidative stress and apoptosis. While they made no mention of the relationship between oral cancer and Cd, they demonstrated that Cd-induced cellular changes in saliva, a critical component of the oral region, cause DNA damage and have a mutagenic properties. Chronic exposure to heavy metals beginning from childhood has been linked to various diseases such as cancer [29]. In summary, although there is compelling evidence that Cd can induce pathological changes in cells in the oral region, there is no conclusive evidence that Cd causes oral malignancy.

Conclusion

Increased Cd concentrations in patients who use tobacco products and have oral cancer are a strong indicator that Cd may be directly related to oral cancer. Additional research is required to determine the role of Cd in tobacco-related oral cancers.

While planning a study to determine the Cd concentrations in biological samples, it is prudent to examine the methodologies of previous studies and to avoid technical deficiencies.

Cd may have a critical role in autophagy and apoptosis. New OSCC cell line studies are required to clarify the relationship between Cd and autophagy-apoptosis.

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Declarations

Conflict of interest The author declare that there is no any financial or non-financial conflict of interest.

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Informed consent Not applicable.

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