Cancer Pathogenesis and Therapy 2 (2024) 215–216

Contents lists available at ScienceDirect

Cancer Pathogenesis and Therapy

journal homepage: www.journals.elsevier.com/cancer-pathogenesis-and-therapy

Letter

Heavy metal exposure as a risk factor in oral cancer

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Managing editor: Peng Lyu

The mortality rate of oral cancer is higher than that of other cancers. There have also been rising concerns regarding exposure to heavy metals and their role in oral cancer development. These heavy metals induce several adverse health effects, including carcinogenesis. This letter examines information on heavy metals from research databases such as PubMed, ScienceDirect, Google Scholar, and ResearchGate, highlighting their toxic mechanism, treatment approaches, and future directions.

Heavy metals are trace elements that affect humans and the environment. Although heavy metals such as zinc and copper aid in intracellular processes by serving as cofactors for enzymes, most elements induce diseases and cancer.[1] Despite severe toxicity, heavy metals are widely used in industries that manufacture products such as paints, vehicles, and batteries. Heavy metals are also used in toys that are handled directly by children.

The inappropriate treatment and disposal of these metals into the environment aid their entry into groundwater, soil, rivers, and other resources. The dissolved forms of these toxic heavy metals ultimately enter the human food chain and cause severe health effects. Numerous studies have indicated that exposure to these compounds gives rise to tumor-suppression genes, disrupts damage-repair mechanisms, and alters enzymatic activity in response to metabolism. A study found an association between the increased risk of cancer in adults and children and the presence of higher concentrations of arsenic and chromium in soil.[2] This underscores the prevalent impact of heavy metals on human health, indicating their dual role as essential micronutrients as well as potential contributors to cancer. The current focus of researchers should be on developing proper management methods for heavy metals and ameliorating their associated adverse health effects.

Oral cancer, accounting for approximately 355,000 cases annually, ranks as the 16th most prevalent malignant neoplasm globally[3] Squamous cell carcinoma accounts for approximately 90% of oral cancers, with two-thirds of these cases occurring in developing nations.[4] The asymptomatic and benign conditions in the early stages of oral cancer prevent patients from seeking early care. Screening offers an opportunity for early detection of this cancer. In most oral cancer cases, patients undergo a premalignant phase, where screening captures oral potentially malignant disorders. This group of disorders is associated with an increased risk of oral cancer.

Oral cancer can be classified as malignant or benign. Malignant oral cavity tumors include squamous cell carcinoma, with cells described as infiltrative, exophytic, verrucous, ulcerated, or flat. Another type of cancer are rare tumors involving different cells, such as those of the salivary gland, bone, and lymphatic system. Some benign conditions include oral leukoplakia, lichen planus, fibroma, papilloma, and mucocele. Overall, early detection and appropriate intervention are possible by following an effective screening and classification strategy for oral cancer.

The interaction of metal ions with cellular components such as DNA and proteins causes conformational changes that lead to mutations, apoptosis, or carcinogenesis. The effects of heavy metals on oral cancer are shown in [Figure 1]. Recent studies have indicated that reactive oxygen species (ROS) and oxidative stress play crucial roles in the carcinogenicity of metals. The International Agency for Research on Cancer and the United States Environmental Protection Agency have stated that heavy metals are carcinogenic to humans. This statement is supported by epidemiological and practical studies indicating an association between cases of oral cancer in humans and exposure to heavy metals. A study on the health implications of oral and dermal exposure to heavy metals in borehole water has revealed significant carcinogenic risks for children within a seven-year lifespan, with risk values for nickel (Ni) at 6.23×10^{-4}, lead (Pb) at 3.14×10^{-1}, and chromium (Cr) at 3.53×10^{-3}.[5]

Heavy metals directly influence oral cancer by inducing genotoxicity, oxidative stress, and genetic alterations, and by influencing cellular pathways associated with various diseases. Additionally, these metals modulate the tumor microenvironment and interact with pathways linked to cancer progression. Key toxic mechanisms of heavy metals include disrupting the antioxidant balance, leading to an increase in ROS, and impairing mitochondrial and cellular redox homeostasis. Heavy metals also influence the redox system through ferroptosis. They are associated with tissue damage and increased inflammation in the oral cavity. Exposure to nickel-chromium and copper alloy bridges causes inflammation, resulting in gingivitis or marginal periodontitis.[6]

Some metals are considered carcinogenic because of their ability to induce oxidative damage in oral tissues. For instance, arsenic aids in the growth and multiplication of cancer cells by disrupting signal transduction pathways and stimulating oxidative stress. Oral cancer develops owing to the absorption of arsenic or direct contact with the oral mucosa.[7] The release of toxic cadmium from dental calculus also aids in the development of oral cancer. Varied cadmium levels in the calculus may correlate with oral cancer, as cadmium disrupts DNA repair enzymes by

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https://doi.org/10.1016/j.cpt.2024.05.002
Received 15 April 2024; Received in revised form 15 May 2024; Accepted 23 May 2024

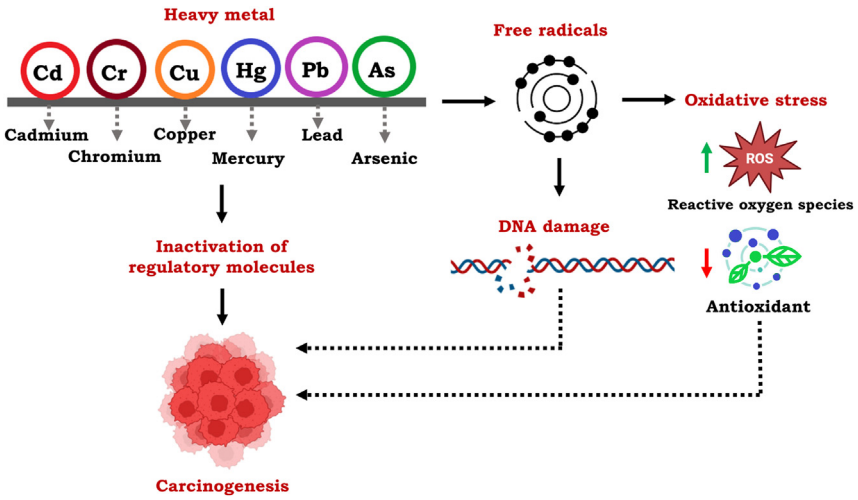

Figure 1. Mechanism through which heavy metals cause toxicity and contribute to carcinogenesis. As: Arsenic; Cd: Cadmium; Cr: Chromium; Cu: Copper; Hg: Mercury; Pb: Lead; ROS: Reactive oxygen species.

replacing zinc, suggesting its role in oral carcinogenesis.[8] Thus, heavy metal toxicity includes cellular dysfunction, inflammation, and carcinogenicity. A better understanding of the mechanism of action would aid in recognizing risks associated with exposure. Regular monitoring and control of the levels of heavy metals and their exposure are critical for preserving optimal health.

The treatment approach for oral cancer associated with heavy metal exposure begins with the diagnosis of oral cancer, involving computed tomography or magnetic resonance imaging to confirm its presence. The second step involves the assessment and removal of heavy metals. The assessment step involves determining heavy metal levels, followed by confirming and eliminating the source of exposure. For instance, chelating medication binds to heavy metals and is released through urine. For oral chelation, a succimer an analog of dimercaprol is used.[9]

Oral cavity treatment generally involves a multidisciplinary approach. Surgery is the ideal treatment for patients with nonmetastatic carcinoma. Adjuvant treatment using chemoradiation is recommended for patients with a high risk of recurrence. In the context of neoadjuvant therapy, systemic therapy can be used to preserve the mandible in patients with advanced disease stages. This therapy is also used in the palliative setting involving non-salvageable locoregional recurrence.[10]

Future directions for understanding the role of heavy metal exposure in oral cancer include research and interventions in several key areas. This includes understanding mechanisms at the molecular level, which would aid in targeted prevention and treatment strategies. Future studies should focus on developing biomarkers associated with heavy metal exposure and oral cancer to achieve early detection, monitoring, and risk stratification. Advancements in precision medicine, including genome profiling, will also aid in identifying individuals susceptible to the carcinogenic effects of heavy metals.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors contribution

Kamalesh Raja: writing - original draft, data curation, and conceptualization; Saravanan Anbalagan: writing - review and editing, methodology, and supervision.

Ethics statement

None.

Data availability statement

The datasets used in the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

References

1. Kim HS, Kim YJ, Seo YR. An overview of carcinogenic heavy metal: molecular toxicity mechanism and prevention. *J Cancer Prev*. 2015;20:232–240. https://doi.org/10.15430/JCP.2015.20.4.232.
2. Kiani B, Hashemi Amin F, Bagheri N, et al. Association between heavy metals and colon cancer: an ecological study based on geographical information systems in North-Eastern Iran. *BMC Cancer*. 2021;21:414. https://doi.org/10.1186/s12885-021-08148-1.
3. Huang Q, Huang Y, Chen C, et al. Prognostic impact of lymphovascular and perineural invasion in squamous cell carcinoma of the tongue. *Sci Rep*. 2023;13:3828. https://doi.org/10.1038/s41598-023-30939-8.
4. Miranda-Filho A, Bray F. Global patterns and trends in cancers of the lip, tongue and mouth. *Oral Oncol*. 2020;102:104551. https://doi.org/10.1016/j.oraloncology.2019.104551.
5. Joseph A, Edet U, Iwok E, Ekanem S. Health implications of the oral and dermal exposure to heavy metals in borehole water from a poorly remediated Ikot Ada Udo community, Akwa Ibom State, South-South Nigeria. *Sci Afr*. 2022;18:e01416. https://doi.org/10.1016/j.sciaf.2022.e01416.
6. Dăguci L, Dăguci C, Dumitrescu CI, et al. Periodontal clinico-morphological changes in patients wearing old nickel–chromium and copper alloys bridges. *Rom J Morphol Embryol*. 2020;61:449–455. https://doi.org/10.47162/RJME.61.2.14.
7. Dhane AS, Sarode SC, Sarode GS, Sharma NK. Rise in arsenic pollution and oral cancer: a call for action. *Oral Oncol Rep*. 2024;9:100238. https://doi.org/10.1016/j.oor.2024.100238.
8. Tavakoli Pirzaman T, Ebrahimi P, Niknezhad S, et al. Toxic mechanisms of cadmium and exposure as a risk factor for oral and gastrointestinal carcinomas. *Hum Exp Toxicol*. 2023;42:09603271231210262. https://doi.org/10.1177/09603271231210262.
9. Flora SJS, Pachauri V. Chelation in metal intoxication. *Int J Environ Res Publ Health*. 2010;7:2745–2788. https://doi.org/10.3390/ijerph7072745.
10. Mohamad I, Glaun MDE, Prabhash K, et al. Current treatment strategies and risk stratification for oral carcinoma. *Am Soc Clin Oncol Educ Book*. 2023;43:e389810. https://doi.org/10.1200/EDBK_389810.