environments

Review

The Emerging Role of Environmental Cadmium Exposure in Prostate Cancer Progression

Rama Saad [1,2], Mohamed Ali Hussein [3,4], Gnanasekar Munirathinam [4] and André Kajdacsy-Balla [2,*]

[1] Department of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN 37232, USA; rama.a.ali@vumc.org
[2] Department of Pathology, University of Illinois at Chicago, Chicago, IL 60612, USA
[3] Institute of Global Health & Human Ecology, School of Sciences and Engineering, American University in Cairo, New Cairo 11835, Egypt; mohamed_hussein@aucegypt.edu
[4] Department of Biomedical Sciences, College of Medicine, University of Illinois, Rockford, IL 61107, USA; mgnanas@uic.edu
* Correspondence: aballa@uic.edu

Abstract: Cadmium (Cd) is a widespread environmental pollutant with several adverse effects on the general population. While Cd is a well-established risk factor for some cancers, such as lung cancer, its impact on prostate cancer (PCa) is not well understood. PCa mortality is associated with its progression to metastatic spread. This underscores the importance of studying the environmental/or molecular factors that govern the progression from organ-confined tumors to widely metastatic disease. To date, most studies addressing the effects of Cd on PCa are focused on the incidence rather than the progression/outcome. Furthermore, most of these epidemiological studies are limited by the small number of samples and the fact that most of these studies measured Cd levels in the air, blood, or urine, which is less applicable for addressing associations in environmental exposure than the measurement of Cd concentrations in the prostate microenvironment. It is still unknown whether Cd is a driver or a consequence of PCa aggressiveness. Addressing the plausibility of causality requires using proper in vitro and in vivo models for sub-micromolar Cd doses that mimic environmental exposure. Most in vitro studies addressing the functional and molecular effects of Cd are limited by the exclusive use of aggressive PCa cell models and very high micromolar unbound Cd concentrations, which are irrelevant for environmental exposure. Significantly, few studies have addressed the effects of sub-micromolar Cd concentrations. Hence, we suggest using nanomolar concentration that resembles real-life exposure, using less aggressive in vitro models such as RWPE-2, employing 3D organoid culture systems, and adopting high throughput-omics techniques, including metallomics, and using transgenic animal models might represent a more effective model. Here, we focus on reports on the impact of Cd on the progression and aggressiveness of already-established PCa instead of on the initial steps of carcinogenesis. We suggest potential future directions for substantiating the plausible link between Cd exposure and PCa aggressiveness.

Keywords: cadmium; prostate cancer; progression; sub-micromolar; environmental

Citation: Saad, R.; Hussein, M.A.; Munirathinam, G.; Kajdacsy-Balla, A. The Emerging Role of Environmental Cadmium Exposure in Prostate Cancer Progression. *Environments* **2024**, *11*, 181. https://doi.org/10.3390/environments11080181

Academic Editor: Peter Brimblecombe

Received: 3 July 2024
Revised: 7 August 2024
Accepted: 9 August 2024
Published: 21 August 2024

1. Introduction

Cadmium (Cd) is a ubiquitous environmental contaminant [1–3]. The general population is exposed to Cd predominantly through dietary routes [3,4]. The low bioavailability of Cd, ≤10%, renders the relative dietary intake of 62 µg/day per 70 Kg person not toxic [4,5]. Certain areas in the world are exceptions to this rule, such as the Jinzu and Kakehashi River basins in Japan, where the soil has very high levels of Cd, which resulted in an increased incidence of Itai-Itai disease [6–8]. Another common exposure route for the general population is inhalation via cigarette smoking. The amount of cadmium absorbed from smoking one pack of cigarettes ranges from 1–3 µg/day, and smokers have urine Cd levels that are twice that of non-smokers [9,10]. Prostate cancer (PCa) is the second leading cause of

cancer death in men in the US [11]. In 2024, it is expected that 35,250 men in the US will die from PCa [11]. PCa mortality is associated with its progression [12]. While PCa is mostly indolent without extraprostatic invasion or metastasis [12], the progression of PCa can be caused by several agents, including androgens [13,14] and environmental agents [15]. Therefore, understanding the environmental/or molecular factors that contribute to PCa progression is of high translational relevance.

While the connection between Cd and PCa has been addressed extensively, the understanding of the role of Cd in PCa progression and mortality remains limited. By comparison, most of the studies investigated the link between Cd and PCa initiation rather than progression [16–19]. Furthermore, some studies that interrogated the effect of Cd on PCa outcome examined Cd levels in urine [8,20,21], which are not as informative about cancer cell Cd exposure as Cd levels in the prostate tissue [22–24]. Similarly, many functional and mechanistic studies on Cd's role in PCa focused on transformation as an early event of carcinogenesis rather than progression [16–19]. In addition, almost all in vitro studies used very high micromolar Cd concentration or cell models originally derived with very high micromolar Cd concentration, which may not represent environmental exposure levels in the prostate.

Here, we offer a comprehensive literature review of the current understanding of the role of Cd in PCa progression. We also highlight the gaps in the field and questions that need to be addressed in future studies.

1.1. Methodology, Literature Review, and Study Selection Criteria

In this review, we searched the literature using the PubMed database following search terms: ((cadmium [TIAB] OR Cd [TIAB]) AND (exposure [TIAB]) AND (progression [TIAB]) AND ("epithelial-mesenchymal transition" [TIAB] OR EMT [TIAB])) AND ("prostatic neoplasms" [TIAB] OR "prostate cancer" [TIAB]). We included all articles that were written in or translated into the English language from 1965 to 2024 and studied the effects of Cd exposure on already-established PCa. Below, we present the findings in epidemiological and experimental studies separately.

1.2. Epidemiological Studies

Some studies attempted to address the role of Cd exposure in PCa outcomes. However, the findings were inconsistent and confounded by factors such as the retrospective design and smoking status. These studies were either population or meta-analysis studies.

A. Population Studies:

While several studies demonstrated an association between Cd exposure and PCa outcome, other studies showed either no association or a non-statistically significant association. This rendered the connection between Cd and PCa outcome unclear. Figure 1 shows a timeline of when these studies were published. We summarize these studies below:

1. Studies that found an association between Cd exposure and PCa outcome:
    i. The earliest evidence for the link between Cd and PCa outcome was documented in occupational populations in 1965 when Potts noticed three out of eight deaths among battery plant workers were due to PCa [25]. This finding set the foundation for epidemiological studies addressing the link between Cd exposure and PCa mortality in battery plant workers.
    ii. A study demonstrated that death from PCa was borderline higher in men who had Cd exposure in male residents of Japan's contaminated Jinzu River basin [8].
    iii. Our recent study addressing the role of environmental Cd exposure and PCa progression showed that air Cd exposure was associated with higher PCa pathological grade and metastasis at the time of diagnosis in nonmetropolitan, urban areas in the United States [26]. In this article, we pointed out that signs of tumor aggressiveness at the time of diagnosis are more reliable tumor

aggressiveness measures than mortality because mortality may depend more on comorbidities attributable to high Cd, disparities in treatment modalities, and access to medical care.

iv. In 2022, another study showed that cumulative 3- and 5-year average concentrations of air Cd are linked to lower PCa survival in a 78,914 PCa population from Pennsylvania [27].

v. Cheung et al. in 2014 attempted to evaluate the NHAHES III dataset for the association between urinary cadmium (U-Cd) and PCa mortality [20]. While the univariate analysis demonstrated an association between U-Cd and PCa mortality, the multivariate analysis lacked statistical significance. They attributed this discrepancy to confounding factors and the few cancer deaths in the population studied.

vi. Bryś et al. demonstrated an association between increased tissue Cd levels in PCa and benign prostatic hyperplasia (BPH) compared to normal tissues [22]. Notably, they reported a decrease in zinc levels in PCa as compared to normal tissues.

vii. Feustel et al. demonstrated a similar pattern in Cd and zinc levels in benign and tumor prostate tissues [28].

viii. To address this question, our group addressed the association between Cd levels in normal-appearing prostate tissue adjacent to cancer and biochemical recurrence after prostatectomy. The data showed that patients in the highest quartile of Cd levels in the normal-appearing area of the prostate have a higher risk of biochemical recurrence [23], favoring the hypothesis that Cd overburden preceded PCa.

ix. In 2023, Tyagi et al. published a study that showed increased cadmium levels in prostate cancer tissues as compared to normal adjacent tissues [24].

While some studies show evidence favoring an association between high Cd levels and PCa progression and outcome [8,20,22,23,25–27], it was unclear whether Cd retention is a consequence or a driver of tumor progression. There is a possibility that Cd retention in PCa tissues is a consequence of altered transport systems in tumor cells (changes in uptake or metabolism) or loss of differentiation in tumor cells. For example, benign prostate epithelium retains zinc, but as cancer cells become less differentiated, zinc is lost, thus favoring Cd accumulation [22,28,29]. To address this question, our group addressed the association between Cd levels in normal-appearing prostate tissue adjacent to cancer and biochemical recurrence after prostatectomy. The data showed that patients in the highest quartile of Cd levels in the normal-appearing area of the prostate have a higher risk of biochemical recurrence [23], thus favoring the hypothesis that Cd overburden precedes PCa.

2. Studies that did not report an association between Cd exposure and PCa outcome:

   i. The Strong Heart Study in American Indians reported a non-significant inverse association between U-Cd levels and PCa mortality [21]. This study had a prospective design and long-term follow-up.

3. Studies that showed a trend for increased PCa mortality:

   i. Another study by Elinder et al. in 1985 showed a non-statistically significant increase in mortality among workers in a Swedish Cd-Nickel battery factory as defined by standardized mortality ratio (SMR) [30].

   ii. In 1979, a study conducted on 269 Cd-Nickel factory workers and 94 Cd-Copper factory workers found a non-statistically significant increase in PCa mortality [31].

4. Limitations and Strengths of Population/Epidemiological Studies:

Several limitations of these studies include (a) the lack of consistency among epidemiological evidence where not all studies found a statistically significant association between Cd burden and PCa mortality or progression, (b) the relatively small numbers of PCa deaths leading to the limited statistical power of several studies. (c) Some studies did

not control tobacco use, a major source of Cd. (d) Most occupational studies are subject to healthy worker bias, where the workforce is likelier to employ and retain healthy subjects. (e) Incomplete follow-up is a significant limitation for occupational studies, especially for diseases such as PCa that have a very long biological history. (f) The retrospective nature of most of these studies. (g) Several studies relied on measuring Cd levels in the air or the fact that soil is rich in Cd rather than measuring Cd levels in the blood, urine, or prostatic tissues. (h) Lack of the ability to control population migration (in studies that use geographic mapping of Cd levels in the environment).

Some of the strengths of these studies include (a) prospective design, such as NHANES III, which allowed for complete follow-up and set within a well-documented cohort; (b) large sample size, such as in the NHANES III; and (c) a long follow-up period, such as in the NHANES III and the Strong Heart Study. (d) Studies such as the NHAHES III and the Strong Heart Study relied on the measurement of U-Cd, which is a good indicator of chronic exposure since it takes years for cessation after exposure [20,21,32]. Furthermore, U-Cd indicates the absorbed dose. However, studies must be expanded since they relied on a single spot urine sample to measure Cd concentrations. In addition, the lack of evidence addressing the correlation between Cd levels in the urine and prostate renders U-Cd limited. Thus, ideally, addressing PCa progression with Cd levels necessitates measuring Cd levels in the tumor microenvironment.

B. Meta-analysis Studies:

More recently, a few meta-analysis studies attempted to address the evidence that Cd exposure is associated with PCa mortality. One analysis addressing the link between Cd exposure and mortality reiterated that very few cohort studies showed an association between Cd and PCa mortality. In contrast, other studies did not find any association. Upon stratification by outcome in this meta-analysis, the odds ratio (OR) for PCa mortality and Cd exposure was 1.29 (95% CI 0.51–3.27) [33].

Another meta-analysis study accumulated 21 studies (12 cohort studies: 5 in the general populations and 7 in occupational populations, 9 case-control studies: 3 in the general populations and 6 in occupational populations). They found that the weighted standardized mortality ratio in occupational populations was 98, with a 95% CI (75–126) for the association between Cd exposure and PCa mortality. In addition, they also looked at PCa mortality upon comparison between the highest and the lowest Cd exposures in the general population, and they found that the weighted relative risk for PCa mortality and Cd exposure was 0.83 (95% CI 0.35–1.98). Thus, in this study, Cd exposure is not linked to PCa mortality [34].

While the meta-analyses had similar conclusions, the possibility that Cd exposure can worsen the PCa outcome or increase its mortality should not be excluded since they were based on studies with several limitations, such as retrospective design, measuring Cd in the air, relying on death certificates to affirm the cause of death, etc.

C. Future directions for epidemiological studies:

Population studies have not provided coherent evidence that Cd is associated with PCa progression and mortality, most likely due to the limitations and confounding factors mentioned above. The lack of solid evidence for this association presents challenges to understanding the role of Cd in PCa outcomes.

Several approaches can be employed to understand the effects of environmental Cd exposure on PCa progression. These approaches include: (A) Conducting large-scale additional prospective population studies. (B) Conducting studies to address whether Cd levels in the urine are positively correlated linearly with prostatic Cd levels or measuring Cd levels in prostatic tissues rather than in urine, which will reflect the Cd levels in tumor microenvironments. (C) Employing a specific measure for PCa aggressiveness/or progression, such as biochemical recurrence after prostatectomy or tumor stage and grade at diagnosis. (D) Developing better bioinformatics and statistical tools for pooling the data from epidemiological studies, and (E) Using cancer-specific measurements for PCa

aggressiveness/or progression, such as post-prostatectomy tumor recurrence and tumor progression during active surveillance. These experimental approaches could be more conclusive than relying on mortality certificates. New approaches are particularly needed for Cd overburden, which is also associated with mortality due to other cancers, cardiovascular diseases, osteoporosis, renal diseases, hypertension, and possibly obesity and diabetes.

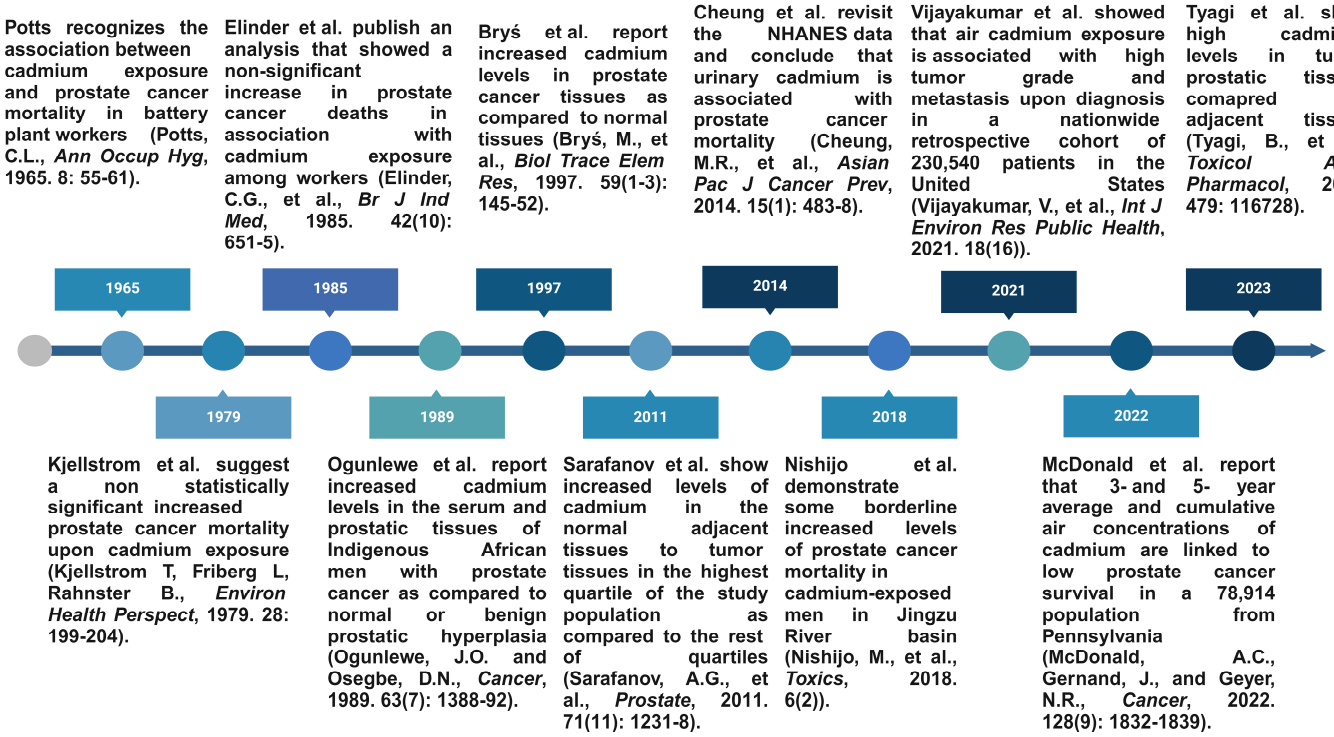

Figure 1. Timeline of epidemiological studies [8,20,22–27,29–31].

1.3. Experimental Evidence

Some studies attempted to test the effects of Cd on PCa progression with experimental tools in vitro and animal studies to establish a more direct cause-and-effect relationship between Cd and PCa. Given that the objective is to understand the role of environmental exposure to Cd on PCa aggressiveness, progression, and/or outcome, the experimental conditions for in vitro and in vivo studies addressing these questions should mimic the same conditions. A major experimental consideration in Cd biology is the dosing system for in vivo studies. While epidemiological studies can guide in vitro concentrations that mimic environmental exposure, defining environmental exposure levels remains controversial. The average Cd concentration in the serum is less than 5 parts per billion (ppb) [35], but only a fraction of it is free Cd, while most of it is bound to metalloproteins, albumin, and other proteins [36]. Here, we define that environmental exposure in vitro should most likely not exceed 10 nM to 100 nM Cd chloride. While this may seem too high of a concentration relative to the blood Cd concentration, we account for the short treatment duration, which ranges from 24 h in 2D cultures to a month in 3D cultures. Advocates of using much higher (micromolar level) exposure to $CdCl_2$ base their decision on the concentration of Cd in contaminated air and water, as well as tissue concentrations of Cd. The toxicity of bound, sequestered Cd is much reduced. For in vivo studies, the amount of Cd exposure is also a complicated task. The Environmental Protection Agency (EPA) set the safety limit of Cd in drinking water at 0.005 mg/L [10]. Cd concentrations in unpolluted waters are mostly less than 1 µg/L [37]. A 2–10 mg $CdCl_2$/L dosing range would be ideal for environmental exposure. While these concentrations are well above environmental exposure, investigators account for the small experimental duration. Previous publication

by Thjiessen et al. demonstrated no detectable renal damage with these doses below 16 weeks of exposure [38].

1. Current Standing of in vitro studies:

In our literature search knowledge, only a few in vitro studies have addressed the role of nanomolar Cd concentration in PCa aggressiveness (Figure 2). Most of the literature addressing the effects of Cd in PCa either focused on cancer initiation and promotion or utilized very high doses that do not mimic environmental exposure.

Cd enters the cells either through voltage-gated calcium channels [39], diffusion [40], or sulfhydryl-sensitive routes [40]. The effects of Cd on the phosphorylation of several kinases associated with increased cell growth have been assessed at nanomolar Cd concentrations. For instance, Cd at nanomolar concentration was associated with increased phosphorylation of MAPK p38, MEK, ERK, JNK, and AKT in 1LN PCa cells [41]. Yet, the mechanism by which Cd mediates phosphorylation and crosstalk of different kinases in PCa remains unclear. Therefore, more studies are warranted. One study demonstrated that Cd decreased the expression of XIAP at post-transcriptional levels in both PC-3 and DU-145 PCa cells [42]. They showed that Cd elicited this effect via an NK-kB-independent proteasomal mechanism. The study used a relatively high micromolar range of Cd concentrations [42]. Table 1 and Figure 2 summarize the current studies relevant to the role of Cd in PCa progression.

Table 1. Summary of experimental studies relevant to the role of Cd in PCa progression with ↑ denotes an increase in the expression level and ↓ denotes a decrease in the expression level of the corresponding marker.

Exposure Mode	Cells Lines	Cd Doses (μM)	Effects	Mechanisms	References
Acute	1LN prostate cells	0.5 μM–1 μM	↑ Cell proliferation	↑ p-MEK1/2, ↑ p-ERK1/2, ↑ p-p38, ↑ p-MAPK, ↑ p-JNK, ↑ p-Akt, and ↑ NFκB	[41]
Acute	PC-3 and DU-145	10 μM, 20 μM, and 30 μM	↑ Sensitivity of cells to TNFσ-mediated apoptosis	↓ XIAP	[42]
Chronic	PC-3 and DU145	0.5 and 2 μM (three months)	↑ Cell migration and ↑ invasion	↑ EMT, ↑ Smad3, ↑ metal metalloproteinase 2, ↓ E-cadherin, and ↑ vimentin, ↑ ER stress, and ↑ ROS	[43]

A recent study showed that chronic Cd exposure resulted in epithelial-mesenchymal transition (EMT) in PCa cells independent from TGF-β [43]. They showed that Cd at 0.5 and 2 μM increased migration and invasion of PCa cells [43]. They attributed this to increased levels of metal metalloproteinase 2 [43]. They also showed chronic exposure (three months) of PCa cells to Cd-induced EMT, evidenced by a decrease in E-cadherin and an increase in vimentin [43].

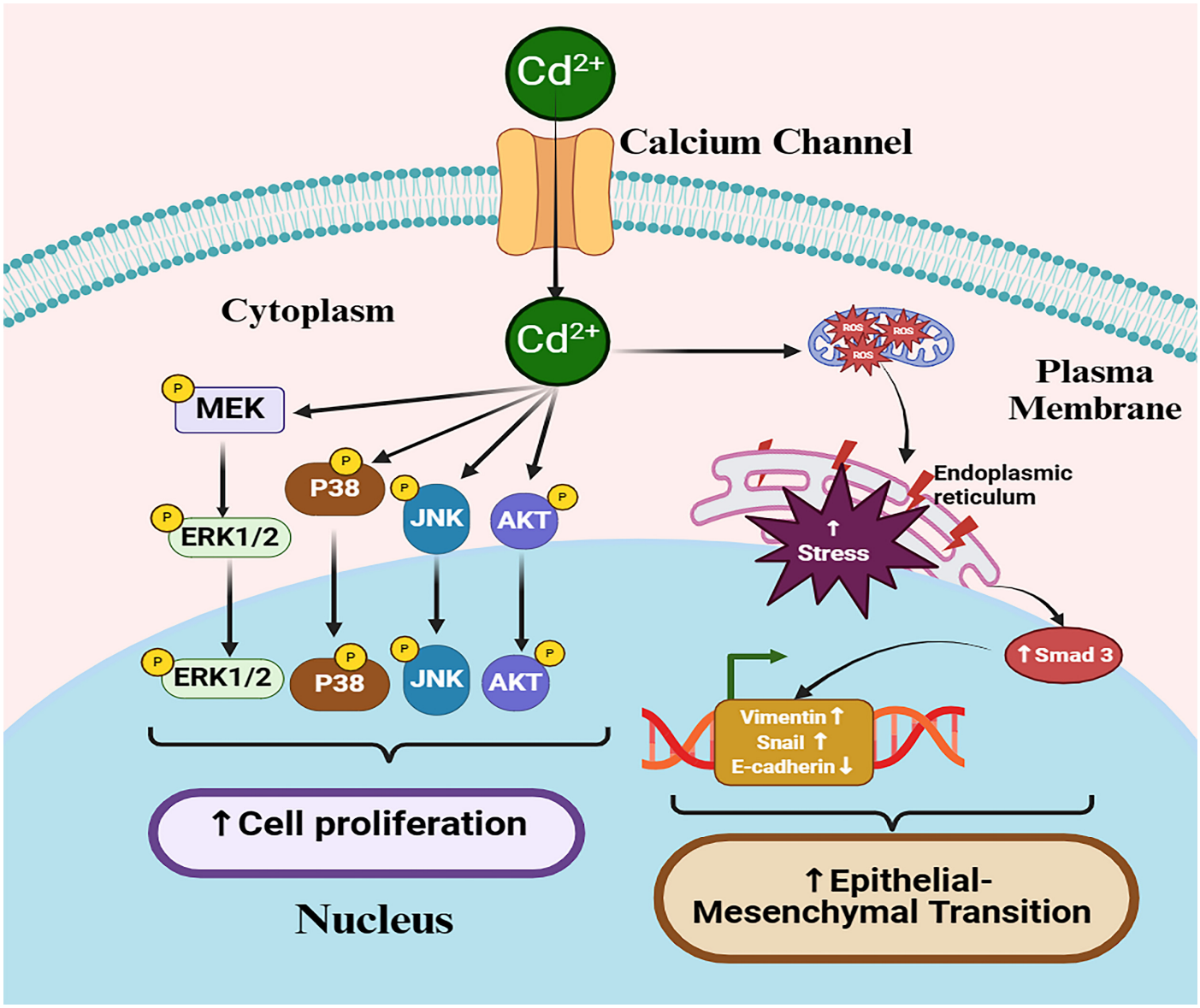

Figure 2. Cartoon illustration emphasizes the significant role of Cd in promoting PCa progression by activating various signaling pathways. Cd ions permeate the cell through calcium channels and activate critical signaling pathways, including MEK (mitogen-activated protein kinase/extracellular signal-regulated kinase) /ERK1/2 (extracellular signal-regulated kinases 1 and 2), P38 (P38 mitogen-activated protein kinase), JNK (c-Jun N-terminal kinase), and AKT (protein kinase B), via phosphorylation, subsequently leading to increased cell proliferation. Cd also triggers the generation of ROS (reactive oxygen species) in the mitochondria, which in turn induces ER (endoplasmic reticulum) stress. Furthermore, ER stress facilitates the translocation of Smad3 (SMAD family member 3) to the nucleus, resulting in the upregulation of EMT (epithelial–mesenchymal transition) markers such as vimentin and Snail and the downregulation of E-cadherin. This collective action promotes EMT. ↑ denotes an increase in the expression level and ↓ denotes a decrease in the expression level of the corresponding marker.

2. Limitations and Future Directions for Experimental Studies:

While several studies have addressed the role of Cd in PCa, most of these studies remain translationally limited in understanding the role of Cd in the progression of already-established PCa. The main limitations for applicability are (1) exceedingly high Cd doses, which, as mentioned previously, do not represent environmental exposure. One approach

to mitigate these limitations is to use nanomolar concentrations that resemble real-life exposure; (2) exclusive use of highly aggressive cells for cell models. To tackle these limitations, employ less aggressive models such as RWPE-2, which would be more translationally relevant to the question of whether Cd promotes PCa progression in men since the tumor is indolent in most men; (3) 2D cell cultures, which fail to represent the tumor microenvironment and its 3D architecture. While the 2D culture systems can help answer many questions, they can present many challenges to recapitulate the in vivo system 3D architecture and simulation of tumor heterogeneity. One way to address these limitations is to employ 3D organoid culture systems, which will allow for testing the effects of Cd in the presence of extracellular cues as represented by laminin and collagen IV. Another way is through 3D co-culture systems between epithelial cells and fibroblasts. This can test for the effects of Cd on proliferation as well as EMT to determine if Cd affects the crosstalk between different cell types; (4) a reductionist approach in addressing the mechanistic implications of Cd (one or a few molecules at a time) instead of a systems biology approach. One potential solution for these limitations is to adopt the high throughput-omics approaches that can help understand the global effects of Cd and establish a network of possible interactions, including metallomics, which enables us to quantify and understand the role of metalloids, such as Cd, in both health and disease, as well as the interaction with other biomolecules, such as metalloproteins and metallometabolites, taking into consideration their expressional and genetic variation [44]. Studies examining the metallomics in PCa and other types of cancer revealed high levels of Cd along with other metalloids, further insinuating the role of Cd in PCa tumorigenesis and progression, thus warranting more investigations in this area [45,46]. Several studies have investigated the role of the metallome as a potential biomarker in different cancers, as well as a method for studying the underlying mechanism of metallodrugs. In addition, integrating machine learning models to aid metallomics profiling will pave the way for a deep understanding of the role of Cd in cancer progression [47–51]; and (5) the lack of animal studies addressing the role of Cd on PCa progression, where most studies focused on the role of Cd in PCa induction [18,19].

While mimicking environmental exposure to Cd is not very difficult using mice models, since adding Cd to the water is an ideal route, the choice of the perfect model remains a challenge. While nude mice and severe combined immune-deficient (SCID) mice remain valuable for the uptake of tumor cells, these systems are challenged to simulate human immune systems. Other models available include the Lo-MYC and Hi-MYC mice models, which represent orthotopic models, where Cd exposure can be controlled at specific tumor stages. However, these models fail to represent the tumor heterogeneity implicated by inter-individual and intra-individual tumor variations and mutations. Other models, such as the transgenic adenocarcinoma of the mouse prostate (TRAMP), lung adenocarcinoma-derived YAP (LADY), and Nkx3.1 models, represent more aggressive tumors.

2. Conclusions

While there is a growing body of evidence that environmental exposure to Cd is associated with PCa progression, outcome, and/or mortality, there is a lack of a consistent direct association, possibly owing to several limitations in population studies, meta-analysis studies, and experimental work. Addressing these gaps will address the question of whether men with higher exposure to environmental Cd are more likely to die from PCa or not. Furthermore, this work may help investigators lay the foundation for future studies addressing the effects of Cd chelation or blocking of effects on targets as a preventive measure for PCa progression.

Author Contributions: Conceptualization: R.S., M.A.H., G.M. and A.K.-B. Methodology: R.S., M.A.H., G.M. and A.K.-B. Literature review: R.S. and M.A.H. Data collection: R.S. and M.A.H. Writing—Original Draft: R.S., M.A.H., G.M. and A.K.-B. Writing—Review and Editing: R.S., M.A.H., G.M. and A.K.-B. Visualization: R.S. and M.A.H. Supervision: G.M. and A.K.-B. Project administration:

A.K.-B. Funding acquisition: A.K.-B. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Chicago Center for Health and EnvironmenT (CACHET) (Grant # P30 ES-027792) and the National Institute of Occupational Safety and Health (NIOSH), University of Illinois at Chicago (T42/OH008672).

Data Availability Statement: No new data were created or analyzed in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Guo, H.; Hu, R.; Huang, G.; Pu, W.; Chu, X.; Xing, C.; Zhang, C. Molybdenum and cadmium co-exposure induces endoplasmic reticulum stress-mediated apoptosis by Th1 polarization in Shaoxing duck (*Anas platyrhyncha*) spleens. *Chemosphere* **2022**, *298*, 134275. [CrossRef] [PubMed]
2. Zhang, C.; Hu, Z.; Hu, R.; Pi, S.; Wei, Z.; Wang, C.; Yang, F.; Xing, C.; Nie, G.; Hu, G. New insights into crosstalk between pyroptosis and autophagy co-induced by molybdenum and cadmium in duck renal tubular epithelial cells. *J. Hazard. Mater.* **2021**, *416*, 126138. [CrossRef] [PubMed]
3. Horiguchi, H.; Oguma, E.; Sasaki, S.; Miyamoto, K.; Ikeda, Y.; Machida, M.; Kayama, F. Dietary exposure to cadmium at close to the current provisional tolerable weekly intake does not affect renal function among female Japanese farmers. *Environ. Res.* **2004**, *95*, 20–31. [CrossRef] [PubMed]
4. Substances, A.F.T.; Disease, R. How Are People Exposed to Cadmium? Available online: https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=https://www.atsdr.cdc.gov/csem/cadmium/How-Are-People-Exposed-to-Cadmium.html&ved=2ahUKEwjt5v_4o4OIAxXI6DQHHUdjCY8QFnoECBQQAQ&usg=AOvVaw1HbOE9I39fzhwReO-Bn2iP (accessed on 21 March 2024).
5. Satarug, S.; Vesey, D.A.; Gobe, G.C. Health Risk Assessment of Dietary Cadmium Intake: Do Current Guidelines Indicate How Much is Safe? *Environ. Health Perspect.* **2017**, *125*, 284–288. [CrossRef] [PubMed]
6. Kobayashi, E.; Suwazono, Y.; Uetani, M.; Inaba, T.; Oishi, M.; Kido, T.; Nishijo, M.; Nakagawa, H.; Nogawa, K. Estimation of benchmark dose for renal dysfunction in a cadmium non-polluted area in Japan. *J. Appl. Toxicol. JAT* **2006**, *26*, 351–355. [CrossRef] [PubMed]
7. Ezaki, T.; Tsukahara, T.; Moriguchi, J.; Furuki, K.; Fukui, Y.; Ukai, H.; Okamoto, S.; Sakurai, H.; Honda, S.; Ikeda, M. Analysis for threshold levels of cadmium in urine that induce tubular dysfunction among women in non-polluted areas in Japan. *Int. Arch. Occup. Environ. Health* **2003**, *76*, 197–204. [CrossRef] [PubMed]
8. Nishijo, M.; Nakagawa, H.; Suwazono, Y.; Nogawa, K.; Sakurai, M.; Ishizaki, M.; Kido, T. Cancer Mortality in Residents of the Cadmium-Polluted Jinzu River Basin in Toyama, Japan. *Toxics* **2018**, *6*, 23. [CrossRef] [PubMed]
9. Mannino, D.M.; Holguin, F.; Greves, H.M.; Savage-Brown, A.; Stock, A.L.; Jones, R.L. Urinary cadmium levels predict lower lung function in current and former smokers: Data from the Third National Health and Nutrition Examination Survey. *Thorax* **2004**, *59*, 194–198. [CrossRef] [PubMed]
10. Substances, A.f.T.; Disease, R. Public Health Statement for Cadmium. Available online: https://wwwn.cdc.gov/TSP/PHS/PHS.aspx?phsid=46&toxid=15 (accessed on 12 May 2023).
11. Society, A.C. Key Statistics for Prostate Cancer. Available online: https://www.cancer.org/cancer/types/prostate-cancer/about/key-statistics.html (accessed on 12 February 2023).
12. Merriel, S.W.D.; May, M.T.; Martin, R.M. Predicting prostate cancer progression: Protocol for a retrospective cohort study to identify prognostic factors for prostate cancer outcomes using routine primary care data. *BMJ Open* **2018**, *8*, e019409. [CrossRef]
13. Dai, C.; Heemers, H.; Sharifi, N. Androgen Signaling in Prostate Cancer. *Cold Spring Harb. Perspect. Med.* **2017**, *7*, a030452. [CrossRef]
14. Desai, K.; McManus, J.M.; Sharifi, N. Hormonal Therapy for Prostate Cancer. *Endocr Rev* **2021**, *42*, 354–373. [CrossRef] [PubMed]
15. Wei, Y.; He, H.; Han, T.; Wang, B.; Ji, P.; Wu, X.; Qian, J.; Shao, P. Environmental explanation of prostate cancer progression based on the comprehensive analysis of perfluorinated compounds. *Ecotoxicol Environ Saf* **2023**, *263*, 115267. [CrossRef] [PubMed]
16. Kolluru, V.; Pal, D.; Papu John, A.M.S.; Ankem, M.K.; Freedman, J.H.; Damodaran, C. Induction of Plac8 promotes pro-survival function of autophagy in cadmium-induced prostate carcinogenesis. *Cancer Lett.* **2017**, *408*, 121–129. [CrossRef] [PubMed]
17. Kolluru, V.; Tyagi, A.; Chandrasekaran, B.; Ankem, M.; Damodaran, C. Induction of endoplasmic reticulum stress might be responsible for defective autophagy in cadmium-induced prostate carcinogenesis. *Toxicol. Appl. Pharmacol.* **2019**, *373*, 62–68. [CrossRef] [PubMed]
18. Waalkes, M.P.; Anver, M.R.; Diwan, B.A. Chronic toxic and carcinogenic effects of oral cadmium in the Noble (NBL/Cr) rat: Induction of neoplastic and proliferative lesions of the adrenal, kidney, prostate, and testes. *J. Toxicol. Environ. Health. Part A* **1999**, *58*, 199–214. [CrossRef]
19. Waalkes, M.P.; Rehm, S.; Riggs, C.W.; Bare, R.M.; Devor, D.E.; Poirier, L.A.; Wenk, M.L.; Henneman, J.R.; Balaschak, M.S. Cadmium carcinogenesis in male Wistar [Crl:(WI)BR] rats: Dose-response analysis of tumor induction in the prostate and testes and at the injection site. *Cancer Res.* **1988**, *48*, 4656–4663.

20. Cheung, M.R.; Kang, J.; Ouyang, D.; Yeung, V. Association between urinary cadmium and all cause, all cancer and prostate cancer specific mortalities for men: An analysis of national health and nutrition examination survey (NHANES III) data. *Asian Pac. J. Cancer Prev. APJCP* **2014**, *15*, 483–488. [CrossRef] [PubMed]
21. García-Esquinas, E.; Pollan, M.; Tellez-Plaza, M.; Francesconi, K.A.; Goessler, W.; Guallar, E.; Umans, J.G.; Yeh, J.; Best, L.G.; Navas-Acien, A. Cadmium exposure and cancer mortality in a prospective cohort: The strong heart study. *Environ. Health Perspect.* **2014**, *122*, 363–370. [CrossRef]
22. Bryś, M.; Nawrocka, A.D.; Miekoś, E.; Zydek, C.; Foksiński, M.; Barecki, A.; Krajewska, W.M. Zinc and cadmium analysis in human prostate neoplasms. *Biol. Trace Elem. Res.* **1997**, *59*, 145–152. [CrossRef]
23. Sarafanov, A.G.; Todorov, T.I.; Centeno, J.A.; Macias, V.; Gao, W.; Liang, W.M.; Beam, C.; Gray, M.A.; Kajdacsy-Balla, A.A. Prostate cancer outcome and tissue levels of metal ions. *Prostate* **2011**, *71*, 1231–1238. [CrossRef]
24. Tyagi, B.; Chandrasekaran, B.; Tyagi, A.; Shukla, V.; Saran, U.; Tyagi, N.; Talluri, S.; Juneau, A.D.; Fu, H.; Ankem, M.K.; et al. Exposure of environmental trace elements in prostate cancer patients: A multiple metal analysis. *Toxicol. Appl. Pharmacol.* **2023**, *479*, 116728. [CrossRef]
25. Potts, C.L. Cadmium proteinuria—The health of battery workers exposed to cadmium oxide dust. *Ann. Occup. Hyg.* **1965**, *8*, 55–61. [CrossRef]
26. Vijayakumar, V.; Abern, M.R.; Jagai, J.S.; Kajdacsy-Balla, A. Observational Study of the Association between Air Cadmium Exposure and Prostate Cancer Aggressiveness at Diagnosis among a Nationwide Retrospective Cohort of 230,540 Patients in the United States. *Int. J. Environ. Res. Public Health* **2021**, *18*, 8333. [CrossRef]
27. McDonald, A.C.; Gernand, J.; Geyer, N.R. Ambient air exposures to arsenic and cadmium and overall and prostate cancer-specific survival among prostate cancer cases in Pennsylvania, 2004 to 2014. *Cancer* **2022**, *128*, 1832–1839. [CrossRef]
28. Feustel, A.; Wennrich, R.; Steiniger, D.; Klauss, P. Zinc and cadmium concentration in prostatic carcinoma of different histological grading in comparison to normal prostate tissue and adenofibromyomatosis (BPH). *Urol. Res.* **1982**, *10*, 301–303. [CrossRef]
29. Ogunlewe, J.O.; Osegbe, D.N. Zinc and cadmium concentrations in indigenous blacks with normal, hypertrophic, and malignant prostate. *Cancer* **1989**, *63*, 1388–1392. [CrossRef]
30. Elinder, C.G.; Kjellström, T.; Hogstedt, C.; Andersson, K.; Spång, G. Cancer mortality of cadmium workers. *Br. J. Ind. Med.* **1985**, *42*, 651–655. [CrossRef]
31. Kjellström, T.; Friberg, L.; Rahnster, B. Mortality and cancer morbidity among cadmium-exposed workers. *Environ. Health Perspect.* **1979**, *28*, 199–204. [CrossRef]
32. Adams, S.V.; Passarelli, M.N.; Newcomb, P.A. Cadmium exposure and cancer mortality in the Third National Health and Nutrition Examination Survey cohort. *Occup. Environ. Med.* **2012**, *69*, 153–156. [CrossRef]
33. Ju-Kun, S.; Yuan, D.B.; Rao, H.F.; Chen, T.F.; Luan, B.S.; Xu, X.M.; Jiang, F.N.; Zhong, W.D.; Zhu, J.G. Association Between Cd Exposure and Risk of Prostate Cancer: A PRISMA-Compliant Systematic Review and Meta-Analysis. *Medicine* **2016**, *95*, e2708. [CrossRef]
34. Chen, C.; Xun, P.; Nishijo, M.; Carter, S.; He, K. Cadmium exposure and risk of prostate cancer: A meta-analysis of cohort and case-control studies among the general and occupational populations. *Sci. Rep.* **2016**, *6*, 25814. [CrossRef]
35. Wroblewski, K.; Wojnicka, J.; Tutka, P.; Szmagara, A.; Blazewicz, A. Measurements of cadmium levels in relation to tobacco dependence and as a function of cytisine administration. *Sci. Rep.* **2024**, *14*, 1883. [CrossRef]
36. Webb, M.; Cain, K. Functions of metallothionein. *Biochem. Pharmacol.* **1982**, *31*, 137–142. [CrossRef]
37. WHO. *Cadmium in Drinking-Water*; WHO: Geneva, Switzerland, 2011. Available online: https://cdn.who.int/media/docs/default-source/wash-documents/wash-chemicals/cadmium.pdf?sfvrsn=4dd545bd_4 (accessed on 2 July 2024).
38. Thijssen, S.; Maringwa, J.; Faes, C.; Lambrichts, I.; Van Kerkhove, E. Chronic exposure of mice to environmentally relevant, low doses of cadmium leads to early renal damage, not predicted by blood or urine cadmium levels. *Toxicology* **2007**, *229*, 145–156. [CrossRef]
39. Cui, Z.G.; Ahmed, K.; Zaidi, S.F.; Muhammad, J.S. Ins and outs of cadmium-induced carcinogenesis: Mechanism and prevention. *Cancer Treat. Res. Commun.* **2021**, *27*, 100372. [CrossRef]
40. Hinkle, P.M.; Kinsella, P.A.; Osterhoudt, K.C. Cadmium uptake and toxicity via voltage-sensitive calcium channels. *J. Biol. Chem.* **1987**, *262*, 16333–16337.
41. Misra, U.K.; Gawdi, G.; Pizzo, S.V. Induction of mitogenic signalling in the 1LN prostate cell line on exposure to submicromolar concentrations of cadmium+. *Cell Signal.* **2003**, *15*, 1059–1070. [CrossRef]
42. Golovine, K.; Makhov, P.; Uzzo, R.G.; Kutikov, A.; Kaplan, D.J.; Fox, E.; Kolenko, V.M. Cadmium down-regulates expression of XIAP at the post-transcriptional level in prostate cancer cells through an NF-kappaB-independent, proteasome-mediated mechanism. *Mol. Cancer* **2010**, *9*, 183. [CrossRef]
43. Hu, W.; Xia, M.; Zhang, C.; Song, B.; Xia, Z.; Guo, C.; Cui, Y.; Jiang, W.; Zhang, S.; Xu, D.; et al. Chronic cadmium exposure induces epithelial mesenchymal transition in prostate cancer cells through a TGF-β-independent, endoplasmic reticulum stress induced pathway. *Toxicol. Lett.* **2021**, *353*, 107–117. [CrossRef]
44. Callejon-Leblic, B.; Arias-Borrego, A.; Pereira-Vega, A.; Gomez-Ariza, J.L.; Garcia-Barrera, T. The Metallome of Lung Cancer and its Potential Use as Biomarker. *Int. J. Mol. Sci.* **2019**, *20*, 778. [CrossRef]
45. Zhang, Y.; He, J.; Jin, J.; Ren, C. Recent advances in the application of metallomics in diagnosis and prognosis of human cancer. *Metallomics* **2022**, *14*, mfac037. [CrossRef] [PubMed]

46. Keltie, E.; Hood, K.M.; Cui, Y.; Sweeney, E.; Ilie, G.; Adisesh, A.; Dummer, T.; Bharti, V.; Kim, J.S. Arsenic Speciation and Metallomics Profiling of Human Toenails as a Biomarker to Assess Prostate Cancer Cases: Atlantic PATH Cohort Study. *Front. Public Health* **2022**, *10*, 818069. [CrossRef]
47. Hood, K.M.; Sweeney, E.; Ilie, G.; Keltie, E.; Kim, J.S. Toenail arsenic species and metallome profiles associated with breast, cervical, prostate, and skin cancer prevalence in the Atlantic Partnership for Tomorrow's Health cohort. *Front. Public Health* **2023**, *11*, 1148283. [CrossRef]
48. Chen, Z.; Liu, X.; Wang, W.; Zhang, L.; Ling, W.; Wang, C.; Jiang, J.; Song, J.; Liu, Y.; Lu, D.; et al. Machine learning-aided metallomic profiling in serum and urine of thyroid cancer patients and its environmental implications. *Sci. Total Environ.* **2023**, *895*, 165100. [CrossRef] [PubMed]
49. Gabbiani, C.; Magherini, F.; Modesti, A.; Messori, L. Proteomic and metallomic strategies for understanding the mode of action of anticancer metallodrugs. *Anticancer Agents Med. Chem.* **2010**, *10*, 324–337. [CrossRef] [PubMed]
50. Lee, M.H.; Gao, Y.T.; Huang, Y.H.; McGee, E.E.; Lam, T.; Wang, B.; Shen, M.C.; Rashid, A.; Pfeiffer, R.M.; Hsing, A.W.; et al. A Metallomic Approach to Assess Associations of Serum Metal Levels with Gallstones and Gallbladder Cancer. *Hepatology* **2020**, *71*, 917–928. [CrossRef]
51. Ossolinski, K.; Ruman, T.; Copie, V.; Tripet, B.P.; Nogueira, L.B.; Nogueira, K.; Kolodziej, A.; Plaza-Altamer, A.; Ossolinska, A.; Ossolinski, T.; et al. Metabolomic and elemental profiling of blood serum in bladder cancer. *J. Pharm. Anal.* **2022**, *12*, 889–900. [CrossRef]