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Research Article

Multivariate Statistical Assessment of Metal Exposure in Fingernails of Women with Cervical Cancer

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ABSTRACT

Purpose: This study aimed to evaluate the association between trace metal exposure and the risk of cervical cancer in Vietnamese women using fingernail elemental profiling and multivariate statistical methods.

Methods: Fingernail samples were collected from 61 women diagnosed with cervical cancer and 43 healthy controls. Concentrations of eight metals—including Cr, Mn, Fe, Cu, Zn, As, Se, and Pb—were quantified using total reflection X-ray fluorescence (TXRF) spectrometry. Multivariable logistic regression was applied to estimate the odds ratios (ORs) for predicting increased risks of cervical cancer. In addition, Spearman correlation analysis and principal component analysis (PCA) were used to explore the associations among metals, demographic factors, and geographic regions.

Results: The concentrations of Cr, Mn, Cu, As, and Pb in fingernails were significant predictors of an increased risk of cervical cancer. As and Pb showed the strongest associations, with ORs of 7.11 and 5.89, respectively ($p < 0.001$). In contrast, Zn demonstrated a protective effect (OR < 1; $p = 0.0011$). The model showed excellent discriminative power (AUC = 0.963), with high sensitivity (0.814) and specificity (0.984). Correlation analyses revealed distinct patterns of metal accumulation across age groups and regions and suggested complex inter-element interactions. PCA confirmed that age and region of residence influenced the metal profiles, supporting their utility in exposure assessments.

Conclusion: Fingernail analysis combined with multivariate statistics provides a practical approach for evaluating chronic metal exposure and its association with an increased risk of cervical cancer. This method may contribute to biomonitoring efforts and risk stratification in environmental health studies.

Key words: Cervical cancer, fingernail, trace metal, TXRF, logistic regression, correlation analysis, principal component analysis

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INTRODUCTION

Cervical cancer, a largely preventable disease, is one of the most common types of cancer in women worldwide. According to the World Health Organization (WHO), there were approximately 660,000 new cases of cervical cancer and 350,000 associated deaths in 2022, with over 85% of deaths occurring in low- and middle-income countries [1]. In Vietnam, cervical cancer ranks second among known cancers in women, especially in the 15–44 age group, with approximately 4,600 new cases and 2,570 deaths each year [2].

The leading cause of cervical cancer is persistent infection with human papillomavirus (HPV). Other risk factors, such as smoking, multiple childbirths, the prolonged use of contraceptives, a weakened immune system, poor nutrition, and exposure to harmful environmental factors, also contribute to an increased risk of developing the disease [3,4]. Further, increasing evidence has suggested that exposure to heavy metals is a potential risk factor in the carcinogenic process by promoting oxidative stress, DNA damage, and immune dysfunction [5–8].

Previous studies have used various biological samples to assess levels of metal exposure, including blood, serum, tissue, urine, and hair. However, each sample type has limitations; for example, blood and serum reflect only short-term exposure, tissue requires invasive collection methods, and hair is subject to religious and ethnic considerations [9–11].

In recent years, fingernails have emerged as a promising biological indicator for assessing long-term metal exposure. Given their keratin-rich composition, fingernails grow at a rate of approximately 3 mm per month. Due to their secure, long-term nature, they accumulate metals over time and are less affected by immediate changes in the body's environment. Further, the noninvasive nature of fingernail collection ensures participant or volunteer comfort, making it

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a convenient process that offers easy storage. These factors make fingernails an attractive option for biological monitoring among researchers [12,13].

Many research efforts have used fingernails to assess metal exposure in occupational health, neurological disorders, and cancer research [14–18]. However, studies analyzing the relationship between metal exposure and the risk of cervical cancer using fingernail samples are still limited. Additionally, several studies have employed statistical and chemometric approaches to enhance the understanding of the interactions and sources of metals in biological matrices. For instance, principal component analysis (PCA) and hierarchical cluster analysis (HCA) have been widely used to classify exposure groups and identify possible sources of heavy metals in hair, blood, and nail samples [19–21]. Univariate and multivariate statistical analyses, including the t-test, ANOVA, correlation analysis, and logistic regression models, have also been employed to explore the relationships between metal concentrations and health outcomes in different populations [22–25]. Nevertheless, there is still a lack of systematic research combining these statistical tools to evaluate the contribution of multiple factors (such as age, environment, and lifestyle) to metal exposure in cervical cancer patients.

In previous work, we investigated the elemental composition of the fingernails of women with cervical cancer and compared it with that of unaffected women,[18] noting high concentrations of essential metals (Mn, Fe, and Cu) and toxic metals (Cr, As, and Pb) in the fingernails of cervical cancer patients. Conversely, essential metals such as Ca, Zn, and Se were found at lower concentrations in cervical cancer patients compared to the healthy control group. The correlation between metals was also examined to assess their interactions. However, the study presented limitations, given that it did not investigate the contributions of other factors, such as patients' age and living environments, to metal exposure in fingernail samples.

To expand on our previous work, the current study aims to (i) evaluate the risk of exposure to certain metals in the fingernails of women with cervical cancer using multivariable logistic regression and (ii) assess the correlation between metal concentrations and risk factors, such as age and living environment, using multivariable statistical methods.

MATERIALS AND METHODS

Preparation and cleaning of fingernail samples

After presenting the research purpose (regarding metal exposure in the fingernails of women with cervical cancer) and committing to ensuring the confidentiality of patient and participant information, this study was approved by the Scientific Council of the Ho Chi Minh City Oncology Hospital and the volunteers. Previous studies have detailed the processes of collecting and cleaning fingernail samples [15–18]. Table 1 summarizes the information on the collected fingernail samples. The primary difference between this study and previous studies was the sample size of the patient group (61 vs. 40), with age and region of residence each divided into four subgroups.

Preparation of samples for TXRF analysis

The fingernail samples were first washed with acetone and distilled water and dried at 40 °C for 10 minutes. In the TXRF analysis, the fingernail samples were digested to form sample solutions; our recent publication [18] provides a detailed account of the sample digestion process.

TXRF spectrometer system

In this study, an automated elemental analysis system, the S2 PICOFOX TXRF spectrometer (Bruker, Germany), was used. The system performs the qualitative and quantitative analysis of multiple elements from Al to U, with detection limits typically in the ppm range and capable of reaching ppb levels in some cases [17,18]. The TXRF spectrometer consists of an X-ray tube with a Mo anode (K_a = 17.5 keV) operating at 50 kV and 202 μA, combined with a silicon drift detector (SDD) with a full width at half maximum (FWHM) of 135.94 eV at the Mn-K_a peak. The data collection and analysis were performed using the integrated Spectra 7 software in the S2 PICOFOX control system. Phuong et al. [17] have previously confirmed the detection limit, repeatability, and accuracy of elemental concentration analysis in fingernail samples using this TXRF spectrometer system. Five samples were analyzed per run; the measurements of all fingernail and standard samples were performed in triplicate, each lasting 600 seconds [18].

Statistical analysis

Odds, odds ratio (OR), logit, and multivariate logistic regression model

In epidemiological and biomedical studies, the probability of an event occurring (e.g., developing cervical cancer) is denoted by P, while the probability of the event not occurring is $(1 - P)$. The ratio of these two probabilities is called the *odds*, defined as in Equation 1:

$$Odds = \frac{P}{1-P} \quad (1)$$

Table 1: Summary of information on samples collected from participating subjects.

Information		Patient group	Control group
Sex		Female	Female
Age (Mean ± SD)(*)		30 – 75 (54.7 ± 11.4)	26 – 78 (53.4 ± 12.3)
Sample number		61	43
Age range (Age group label)	≤35 (Age_1)	10	7
	36 – 45 (Age_2)	12	9
	46 – 55 (Age_3)	13	12
	≥56 (Age_4)	22	15
Region (Region label)	Southeast (Region_1)	15	11
	Southwest (Region_2)	31	9
	Central (Region_3)	7	8
	Ho Chi Minh City (Region_4)	8	15
(*) SD = Standard Deviation			

If odds = 1: The probabilities of occurrence and non-occurrence are equal.
If odds > 1: The event is more likely to occur.
If odds < 1: The event is less likely to occur.
When comparing two groups (e.g., exposed vs. unexposed), the *odds ratio* (*OR*) is used to quantify the relationship between the exposure factor and the likelihood of the event (disease), as expressed in Equation 2:

$$OR = \frac{Odds\ in\ exposed\ group}{Odds\ in\ unexposed\ group} = \frac{P_1/(1-P_1)}{P_0/(1-P_0)} \quad (2)$$

If OR = 1: There is no association between exposure and the disease.
If OR > 1: Exposure increases the risk of disease occurrence.
If OR < 1: Exposure may reduce the risk of disease (protective effect).
To statistically model the relationship between the probability of an event and independent variables (continuous or categorical), the *logit function*—the natural logarithm of the odds—is used, as shown in Equation 3:

$$Logit\,(P) = \ln\left(\frac{P}{1-P}\right) \quad (3)$$

The logit function transforms a probability (ranging from 0 to 1) into a continuous variable ranging from –∞ to +∞, allowing for the use of linear regression techniques.
When multiple independent variables are involved (e.g., metal concentrations, age, living environment, etc.), a *multivariate logistic regression model* is employed, expressed as in Equation 4:

$$\log\left(\frac{P}{1-P}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_j X_j \quad (4)$$

Here, P is the probability of the event occurring, and β_j represents the regression coefficients that quantify the relationship between each independent variable X_j and the dependent variable. The *adjusted odds ratio* (*Adj.OR*) is then calculated as in Equation 5:

$$Adj.OR_j = exp\left(\beta_j\right) \quad (5)$$

If Adj.OR_j > 1: An increase in X_j increases the risk of the event.
If Adj.OR_j < 1: An increase in X_j decreases the risk of the event.
If Adj.OR_j = 1: There is no effect on the risk of the event.

Statistical analysis software

Statistical analysis in this study was performed using Origin software (version 2012b, OriginLab Corporation, USA) and R (version 4.4.2, R Development Core Team). Multivariable logistic regression models were used to calculate OR values for predicting cervical cancer risks related to metal exposure, which were analyzed using R. The correlation between the variables of interest was evaluated using the Spearman correlation coefficient, as performed in Origin. PCA was performed in R to identify relationships among the variables of interest.

RESULTS AND DISCUSSION

Assessment of trace metal exposure in relation to risk of cervical cancer

In this study, the contents of eight trace metals (Cr, Mn, Fe, Cu, Zn, As, Se, and Pb) in fingernails were examined. These findings indicate significant differences between cervical cancer patients and the healthy control group ($p < 0.05$), aligning with the results of a previous publication [18]. This level of detail was used to assess the association with an increased risk of cervical cancer, underlining the significance of the research results.

This study employed multivariate logistic regression models to identify prognostic factors linked to an increased risk of cervical cancer in female patients. Additionally, the significance of the variables and prognostic models was evaluated.

After comprehensive adjustment for confounding factors in the multivariable logistic regression model, significant prognostic variables for the risk of cervical cancer were identified. These findings, including the odds ratios, confidence intervals, and p-values, are presented in Table 2 . The results unequivocally point to age and region as demographic factors associated with an increased risk of cervical cancer. An OR < 1 for age indicates that with each unit increase in age, the odds of cervical cancer decrease by 9%; this highlights the higher risk in younger age groups, possibly due to lifestyle choices or early occupational exposure. The regional disparities in risk (OR < 1) suggest that geographical environmental factors or regional lifestyle characteristics influence exposure to or the accumulation of toxic metals.

Metals with an OR > 1, including Cr, Mn, Cu, As, and Pb, were found to be statistically significant. These results provide valuable insights, indicating that individuals with higher concentrations of these metals in their fingernails have higher odds for cervical cancer. Specifically, for each unit increase in the concentrations of Cr, Mn, Cu, As, and Pb, the odds of cervical cancer increase 1.54-, 1.91-, 2.34-, 7.11-, and 5.89-fold, respectively. These metals may be involved in cancer development through various mechanisms, such as oxidative stress, DNA replication disorders, and effects on the methylation cycle of genes [8]. Notably, As and Pb show significantly higher risk, reflecting the role of the long-term accumulation of toxic substances and cancer risk reported in previous epidemiological studies.

In contrast, Zn is a potential protective factor, with an OR < 1 and statistical significance, consistent with its role in protecting the DNA structure, regulating inflammatory responses, and enhancing immunity. This result indicates that individuals with higher Zn concentrations have an 8% lower odds of cervical cancer. Conversely, in this study, the patient group displays lower Zn levels than the control group; thus, the odds of cervical cancer increase by 8%, meaning that individuals with lower Zn concentrations in the body exhibit a higher risk of disease. Similarly, with each unit increase in the concentration of Se (with an OR < 1), the odds of cervical cancer decrease by 64%; this indicates that individuals with Se concentrations lower than normal levels exhibit an increased risk of disease. While Se has a biologically protective role, it does not reach statistical significance in the current model ($p = 0.357$), possibly due to the sample size or interactions with other factors. Fe does not show a significant association in the regression ($p > 0.05$); this suggests that its role in the prognostic model warrants further investigation, highlighting the potential for future research in this area.

Next, Wald statistics were used to assess the relative importance of each variable in the model. Zn (χ^2 = 10.71; p = 0.0011), As (χ^2 = 7.60; p = 0.0058), Pb (χ^2 = 6.58; p = 0.0103), region (χ^2 = 5.68; p = 0.0172), age (χ^2 = 5.14; p = 0.0234), and Cu (χ^2 = 4.87; p = 0.0274) are significant contributors to the model (Figure 1a). Meanwhile, Se, Fe, and Cr do not reach statistical significance, suggesting that their influence is limited or dependent on other interacting factors. This further strengthens the prominent role of Zn and toxic elements such as As and Pb in predicting the risk of cervical cancer in the study group.

Finally, the model's discriminative ability was tested using ROC analysis. The ROC curve, with an area under the curve (AUC) of 0.963 (95% CI: 0.921–0.986), exhibits a significantly high accuracy in distinguishing between the disease and control groups (Figure 1b). The model's optimal cutoff threshold at 0.400 achieves a specificity of 0.814 and a sensitivity of 0.984, indicating the model's potential for initial screenings or clinical diagnostic support. This promising result suggests that the model could be a valuable tool for early detection and intervention in cervical cancer.

Evaluation of correlations between disease-related factors

Spearman correlation analysis indicates statistically significant relationships among demographic factors, regions, and metal concentrations in the fingernail samples of the patient group, reflecting the combined influence of age, living environment, and biological interactions on the absorption and accumulation of metals in the body. The Spearman correlation coefficients between the variables of interest are detailed in Table 3, with Age_1, age group ≤ 35; Age_2, $36 \leq$ age group ≤ 45; Age_3, $46 \leq$ age group ≤ 55; Age_4, age group ≥ 56; Region_1 = Southeast; Region_2 =

Table 2: Adjusted odds ratio (Adj.OR), with a 95% confidence interval, and p-values of prognostic variables in the multivariable logistic regression model for cervical cancer risk.

Variables	Adj.OR (95% CI)	p (LR-test)(*)
Age	0.91 (0.84 - 0.99)	0.013
Region	0.65 (0.45 - 0.94)	0.017
Cr	1.54 (1.05 - 2.26)	< 0.001
Mn	1.91 (1.31 - 2.77)	0.030
Fe	1.01 (0.97 - 1.02)	0.813
Cu	2.34 (1.10 - 4.98)	0.011
Zn	0.92 (0.88 - 0.97)	< 0.001
As	7.11 (2.22 - 22.79)	< 0.001
Se	0.36 (0.04 - 3.66)	0.357
Pb	5.89 (1.52 - 22.86)	0.001
(*) LR-test = Likelihood Ratio test		

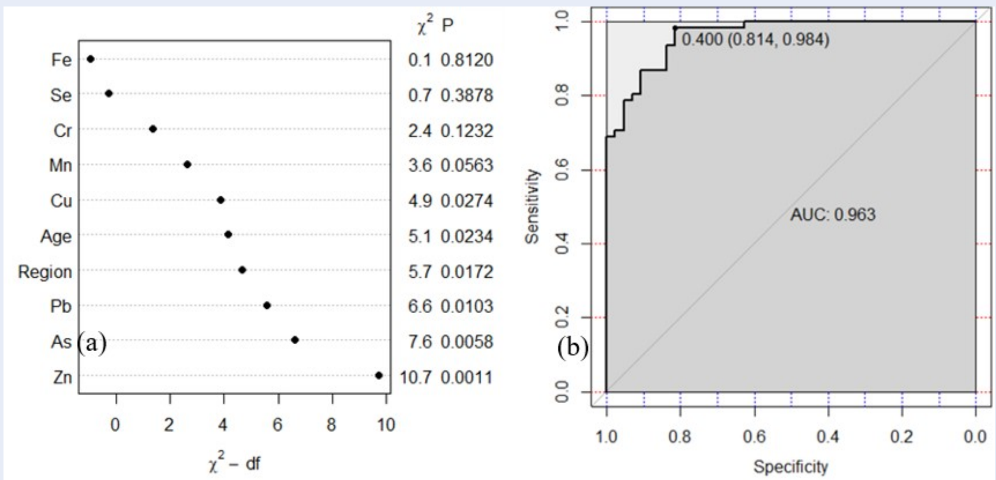

Figure 1: (a) Importance of predictor variables in the logistic regression model. (b) ROC curve and area under the curve (AUC) of the model.

Southwest; Region_3 = Central; and Region_4 = Ho Chi Minh City.

Regarding the relationship between age and metal concentration, Cr, Mn, Fe, Cu, Zn, As, Se, and Pb all show variations across the age groups. Notably, Cr, Mn, and Fe exhibit negative correlations in younger age groups (Age_1, Age_2, and Age_3) and strong positive correlations in the older age group (Age_4), suggesting an increasing accumulation with age or age-related metabolic changes. For example, Cr and Mn show strong positive correlations with Age_4 and negative correlations with Age_2 and Age_3, indicating significant accumulation in the older patient group. Further, there is an inverse trend between Age_2 and Age_4, with a strong negative correlation in Age_2 (r = -0.57) and a strong positive correlation in Age_4 (r = 0.49), possibly reflecting changes in detoxification ability or prolonged exposure. Essential trace metals such as Zn, Cu, and Se also vary with age, showing positive correlations in Age_2 and negative correlations in Age_4, suggesting that aging influences mineral absorption and metabolism. Meanwhile, Pb shows a positive correlation with Age_4, indicating that it accumulates in the body over time.

Considering the region, Cr and Mn are negatively correlated with Region_1, suggesting lower exposure

Table 3: Correlation coefficients between the variables of interest

	Age_1	Age_2	Age_3	Age_4	Region_1	Region_2	Region_3	Region_4	Cr	Mn	Fe	Cu	Zn	As	Se	Pb
Age_1	1.00															
Age_2	-0.09	1.00														
Age_3	-0.10	**-0.26**	1.00													
Age_4	-0.21	**-0.56**	**-0.58**	1.00												
Region_1	-0.11	**0.29**	0.17	**-0.33**	1.00											
Region_2	0.00	-0.09	-0.13	0.18	**-0.58**	1.00										
Region_3	0.22	-0.18	0.06	0.01	-0.21	**-0.37**	1.00									
Region_4	-0.07	-0.07	-0.08	0.15	-0.22	**-0.39**	-0.14	1.00								
Cr	**-0.31**	**-0.31**	-0.14	**0.47**	**-0.30**	0.20	-0.05	0.13	1.00							
Mn	-0.09	**-0.34**	**-0.29**	**0.55**	**-0.29**	0.27	-0.17	0.14	0.51	1.00						
Fe	-0.01	**-0.27**	-0.07	**0.28**	-0.09	0.01	-0.01	0.11	0.20	0.25	1.00					
Cu	-0.03	**0.48**	0.19	**-0.52**	0.11	-0.07	0.03	-0.07	**-0.34**	**-0.4**	**-0.26**	1.00				
Zn	0.11	0.47	0.02	-0.43	0.09	0.00	-0.08	-0.03	**-0.45**	**-0.28**	**-0.47**	**0.37**	1.00			
As	0.07	-0.57	-0.07	0.49	-0.26	0.12	0.08	0.23	**0.30**	**0.42**	**0.37**	**-0.39**	**-0.26**	1.00		
Se	0.24	**0.39**	-0.01	**-0.39**	0.04	-0.12	0.14	-0.01	-0.17	-0.21	-0.13	**0.25**	**0.29**	-0.17	1.00	
Pb	-0.14	-0.25	-0.14	**0.36**	-0.12	**0.33**	**-0.27**	-0.07	**0.42**	**0.38**	0.10	**-0.27**	-0.21	**0.43**	-0.17	1.00

Note: The numbers in bold indicate statistically significant correlations ($p < 0.05$).

or intake levels in this region. In contrast, Mn is positively correlated with Region_2, reflecting differences in environmental conditions or dietary habits between regions. The concentrations of As and Pb decrease in both Region_1 and Region_3, while the Pb concentration increases in Region_2, indicating geographical variations in heavy metal pollution levels.

The correlations between metals reveal a complex interaction network, reflecting the ability to simultaneously absorb from a common exposure source or competitive mechanisms in biological processes. Cr is positively correlated with Mn, As, and Pb and negatively correlated with Cu and Zn, suggesting competitive absorption or counteracting effects in metabolism. Mn shows positive relationships with As and Pb and negative ones with Cu and Zn, indicating conflicts between essential trace metals and toxic metals. In particular, the negative Fe–Cu and Fe–Zn correlations and positive Fe–As relationship indicate cross-regulation between essential minerals and toxic metals. Similarly, Zn displays a negative correlation with As but a positive correlation with Cu and Se, highlighting its regulatory role in mineral balance.

These correlations, especially those between toxic elements (such as As and Pb) and essential minerals, may suggest competitive absorption at the cellular level or the body's adaptive response to metal exposure. This information, therefore, contributes to elucidating the pathogenic mechanisms in diseases related to mineral imbalance, including cancer.

Principal component analysis (PCA) and sample clustering

PCA highlights the main factors influencing the variation of metal concentrations by age and region. Table 4 presents the squared cosine values of the first five principal components, while Figure 2 displays the distribution of variables in the first two principal components (PC1 and PC2). PC1 and PC2 explain 40.06% of the variance, with eigenvalues of 4.57 and 1.83, indicating that they capture significant information in the dataset.

PC1, explaining 28.59% of the variance, shows a strong correlation between the concentrations of several metals (Cr, Mn, Fe, Cu, Zn, Se, As, and Pb) and the Age_2 and Age_4 age groups. These variables have high loadings and the same sign on PC1 (Figure 2), suggesting that in the oldest age group, the concentrations of these metals tend to vary simultaneously. This may reflect metal accumulation over time or age-related physiological changes that increase the absorption or decrease the excretion of these elements. The positive correlations between these metals on PC1 may also indicate familiar pollution sources or similar exposure pathways.

PC2, explaining 11.47% of the variance, mainly distinguishes between the Age_2 age group and Region_2. The high loadings of Age_2 and Region_2 on PC2 indicate significant differences in the metal characteristics of this age group and geographical region compared to other age groups and regions. This could be due to specific environmental factors or separate activities in Region_2 that affect metal accumulation in the Age_2 group.

The PCA squared cosine analysis (Table 4) reveals the complexity of the relationship between metal concentrations in the fingernails of women with cervical cancer and the variables of age and region of residence. PC1, explaining the majority of the variance, reveals the co-variation of several metals (Cr, Mn, Cu, Zn, As, Fe, Se, and Pb) and significant contributions from the oldest (Age_4) and second (Age_2) age groups, suggesting the role of metal accumulation over time and potential age-related biological processes. The subsequent principal components (PC2, PC3, and PC4) are mainly determined by differences among geographical regions (Region_2, Region_3, Region_1, and Region_4), indicating the strong influence of environmental factors and residence locations on metal exposure. Notably, the presence of specific age groups (Age_1 on PC3 and Age_3 on PC4) and region variables indicates an interaction between age and residence region in determining the level of metal exposure. The fifth principal component (PC5) is not dominated by any specific variable, suggesting the presence of unmeasured factors or residual variance. These findings emphasize the importance of considering both age and region of residence in assessing metal exposure in women with cervical cancer; they also suggest the existence of familiar exposure sources for multiple metals and environmental differences between areas. Further research is needed to identify these exposure sources and assess their association with the risk of developing cervical cancer.

While the logistic regression and correlation analyses in this study reveal significant associations between certain trace metals (such as Cr, Mn, Cu, As, and Pb) and cervical cancer, it is essential to note that these findings indicate statistical correlations rather than causal relationships. Individuals with higher concentrations of toxic metals in their fingernails may have increased odds of developing the disease; however, this observation should be interpreted with caution. Several potential confounding factors—such as dietary habits, occupational exposure, family medical histories, environmental pollution, and HPV infection status—were not included in the present model due to data limitations.

Therefore, the present study should be considered an exploratory and hypothesis-generating investigation, primarily aimed at identifying potential associations and providing preliminary insights for future research. Subsequent studies involving larger sample sizes, improved control of confounding variables, and longitudinal designs are required to confirm whether elevated metal concentrations directly contribute to the development of cervical cancer. Integrating molecular biomarkers and HPV genotyping in future work will also help elucidate the underlying biological mechanisms and strengthen causal inferences.

CONCLUSIONS

This study demonstrates a significant association between chronic exposure to trace metals and an increased risk of cervical cancer in Vietnamese women. Elevated concentrations of toxic metals, including As, Pb, Cr, Mn, and Cu, were identified as significant risk

Table 4: Squared cosine ratio of variables in the first principal component, showing the contribution of each variable to the variance structure of the data.

	PC1	PC2	PC3	PC4	PC5
Age_1	0.023	0.010	**0.494**	0.003	0.079
Age_2	**0.415**	0.236	0.085	0.088	0.015
Age_3	0.081	0.262	0.009	**0.311**	0.214
Age_4	**0.647**	0.000	0.003	0.041	0.146
Region_1	0.196	0.108	**0.276**	0.005	0.003
Region_2	0.117	**0.420**	0.011	0.364	0.023
Region_3	0.014	0.185	**0.475**	0.021	0.029
Region_4	0.029	0.018	0.019	**0.444**	0.102
Cr	**0.523**	0.001	0.024	0.021	0.002
Mn	**0.516**	0.095	0.004	0.012	0.007
Fe	**0.341**	0.015	0.000	0.036	0.053
Cu	**0.450**	0.024	0.021	0.004	0.001
Zn	**0.354**	0.231	0.001	0.003	0.056
As	**0.349**	0.028	0.005	0.000	0.241
Se	**0.238**	0.165	0.103	0.066	0.059
	0.284	0.037	0.057	0.018	0.126
Eigenvalue	4.57	1.83	1.59	1.44	1.16
% variance	28.59	11.47	9.91	8.98	7.23
% cumulative of variance	28.59	40.06	49.97	58.94	66.18

Note: The numbers in bold indicate the largest squared cosine value.

factors, while Zn showed a protective effect. These findings support the hypothesis that long-term exposure to specific metals, particularly in environmentally vulnerable or occupationally exposed populations, contributes to the etiology of cervical cancer through oxidative stress, genomic instability, and impaired immune function.

However, it should be emphasized that the present study demonstrates associations rather than causality. Several unmeasured confounders, including dietary habits, occupational exposure, family medical histories, environmental pollution, and HPV infection status, may influence the observed relationships between metal concentrations and the risk of cervical cancer. Therefore, the current results should be interpreted as exploratory and hypothesis-generating, providing preliminary evidence and directions for future studies.

The use of fingernails as a noninvasive biomarker for chronic metal exposure is notably beneficial, as fingernails reflect long-term metal accumulation more accurately than blood or urine. Moreover, the integration of multivariable logistic regression, correlation analysis, and PCA enabled a comprehensive evaluation of risk factors and inter-element relationships. Future research should expand the sample size and geographical coverage, include additional confounding variables, and employ longitudinal or cohort designs to clarify temporal and causal relationships between metal exposure and cancer development. Incorporating molecular biomarkers and HPV genotyping will further elucidate mechanistic pathways and strengthen causal inferences. Such studies will contribute to improved early detection strategies and evidence-based public health interventions for populations that are chronically exposed to metals.

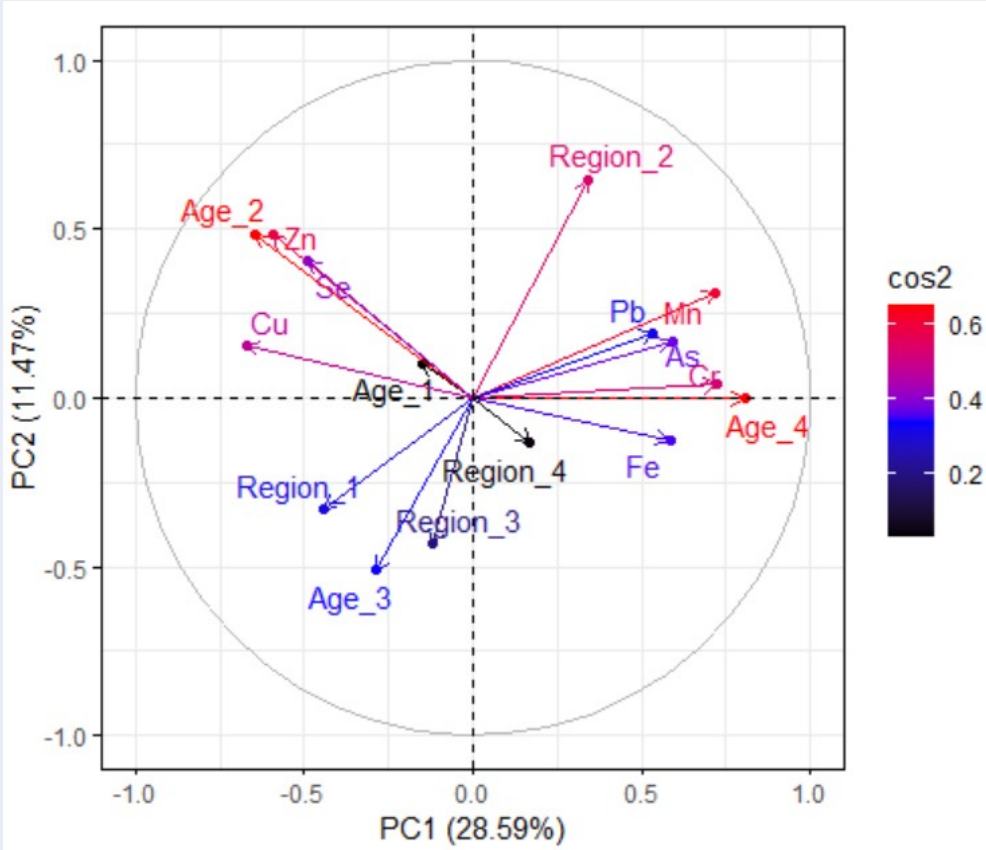

Figure 2: PCA plot of the first two principal components, showing the grouping of samples by age and region based on metal concentrations.

LIST OF ABBREVIATIONS

TXRF: Total Reflection X-Ray Fluorescence
AUC: Area Under the Curve
ROC: Receiver Operating Characteristic
PCA: Principal Component Analysis
DNA: Deoxyribonucleic Acid

AUTHORS' CONTRIBUTIONS

Study concept and design are contributed by Phuong Truc Huynh, Hanh Van Nguyen, and Dong Van Nguyen. Material preparation, data collection, and analysis were performed by Hanh Van Nguyen, Sang Thi Minh Nguyen, Linh Thi Truc Nguyen, Huong Thi Thu Tran, and Loan Thi Hong Truong. The first draft of the manuscript was written by Hanh Van Nguyen, edited by Phuong Truc Huynh, and all authors commented on previous versions of the manuscript. All authors have approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

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ETHICAL APPROVAL

Before the collection of fingernail samples, the purpose of the study was explained to the participants, and they were assured about the anonymity and confidentiality of their responses. All participants gave written informed consent. The study protocol was approved by the Ethics Committee of Ho Chi Minh City Oncology Hospital, Vietnam (Signed October 5, 2022).

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