AUCTORES
Globalize your Research

International Journal of Clinical Case Reports and Reviews
Naoyuki Okamoto*

Open Access

Research Article

Development of A "Cancer Risk" Screening Method Based on Differences in The Balance of Trace Element Concentrations in The Blood Using ICP-MS with A Case-Control Study Approach: Metallo-Balance Method

Naoyuki Okamoto*, Shunsuke Fujimoto, Takuya Shimizu, Mitsuhiro Ueda, Seiichi Inagaki

Health Care Analysis Center, Renatech Co., Ltd., 4-19-15 Takamori, Isehara, Kanagawa 259-1114, Japan.

***Corresponding Author:** Naoyuki Okamoto, Health Care Analysis Center, Renatech Co., Ltd., 4-19-15 Takamori, Isehara, Kanagawa 259-1114, Japan.

Received Date: March 23, 2026 | **Accepted Date:** April 03, 2026 | **Published Date:** April 07, 2026

Citation: Naoyuki Okamoto, Shunsuke Fujimoto, Takuya Shimizu, Mitsuhiro Ueda, Seiichi Inagaki, (2026), Development of A "Cancer Risk" Screening Method Based on Differences in The Balance of Trace Element Concentrations in The Blood Using ICP-MS with A Case-Control Study Approach: Metallo-Balance Method, *International Journal of Clinical Case Reports and Reviews*, 35(1); **DOI:10.31579/2690-4861/1072**

Abstract:

Cancer control is a pressing issue in many countries, and preventing cancer deaths through early detection and treatment is extremely important.

This study conducted a case-control study focusing on trace element concentrations in blood to develop a low-cost, highly accurate, and patient-friendly screening method. Serum samples were collected from 2,912 cancer patients and 5,814 members of the general population. A "risk diagnosis" method was developed using binary logistic regression analysis based on serum concentrations of 17 elements measured using ICP-MS. Efficacy was evaluated using sensitivity, specificity, and AUC. In addition, the incidence of cancer within one year after blood collection was investigated among 7,993 participants in the test period of this method and evaluated using positive predictive values.

The analysis results showed high sensitivity and specificity, with AUCs ranging from 0.737 to 0.993, indicating effective discrimination. Furthermore, the positive predicted values were higher than the theoretical predicted values for pancreatic and prostate cancer in men, and similar to the theoretical predicted values for stomach and colorectal cancer in women.

These results indicate that this method can predict "cancer risk" with high accuracy and is an effective tool for cancer detection.

Key words: trace elements, serum, cancer risk, screening, positive predictive value, case-control study

Introduction

According to Globocan's 2020 report, approximately 20 million people worldwide are diagnosed with cancer each year, and approximately 10 million dies from it. The importance of cancer prevention activities is emphasized in countries around the world, including Japan. These measures can be broadly divided into three categories. Primary prevention aims to reduce the risk of cancer through lifestyle improvements, secondary prevention aims to reduce the risk of death through early detection and treatment of cancer, and tertiary prevention aims to alleviate pain and improve the quality of life for cancer patients [1]

In Japan, cancer control is primarily implemented as secondary prevention, with active screening for five sites: stomach, colorectal, lung, breast, and cervical cancer [2]. In other countries, screening for stomach and lung cancer is not implemented in most countries, and screening mainly focuses on colorectal, breast, and cervical cancer. Japan's colorectal cancer screening rate is low at 24.9%, lower than South Korea's 34.1% and the United States' 52.1%. Similarly, Japan's breast and cervical cancer screening rates are lower than those of South Korea, the United States, and the United Kingdom, posing a significant challenge [3]. Japan aims to achieve a screening rate of over 50% for all cancers, but is currently far from this goal. According to a study by Takeda et al. [4], reasons for not undergoing cancer screening include "I don't think it's necessary because I go to the clinic regularly," "I've been tested before," "I have a health checkup," "I don't have time," and "I'm anxious about the test." These results suggest that awareness of cancer risk is insufficient or that the benefits of cancer screening are not widely recognized.

Currently, cancer screening methods include direct observation and palpation (palpation, endoscopy, etc.) and methods for visualizing the

inside of the body (X-ray, CT scan, MRI, PET scan, etc.). However, visual and palpation methods are limited to the body surface and organs of the digestive tract, imaging diagnostics are expensive and difficult to interpret, and there are problems such as radiation exposure to patients and stress caused by fear and anxiety about undergoing examinations, which has resulted in low screening rates and low patient numbers. Therefore, in recent years, the focus has been on developing new diagnostic methods using bodily fluids such as blood, urine, and saliva, which are called "liquid biopsies," and research is being conducted with the aim of early detection of diseases [5].

We have started research focusing on trace element concentrations in blood. The reason for focusing on trace elements is that while some are essential for living organisms, many have unknown functions or have been reported to have beneficial functions, and it has been suggested that excess or deficiency can inhibit normal biological responses and cause disorders and diseases. Numerous cases have been reported, including anemia due to iron deficiency [6], osteoporosis due to calcium deficiency [7], Minamata disease due to excess organic mercury [8], Keshan disease due to selenium deficiency [9], decreased zinc levels in schizophrenia [10], and decreased magnesium levels and increased phosphorus and calcium levels in heart failure [11]. Regarding cancer, breast cancer patients have been reported to have low serum zinc levels and high calcium, copper, iron, and magnesium levels [12], and breast cancer patients [13] and ovarian cancer patients [14] have also been reported to have high copper/zinc ratios. It has been reported that kidney cancer patients have high cadmium and lead concentrations and low zinc, iron, and manganese concentrations [15]. Furthermore, lung cancer patients have high copper and copper/zinc ratios, but low zinc and iron concentrations [16]. These reports suggest that serum trace element concentrations in diseased patients differ from those in the general population. Focusing on this, we have been developing a new cancer risk diagnostic method for colorectal cancer (men and women), prostate cancer, and breast cancer using blood trace element concentration balances measured by inductively coupled plasma mass spectrometry (ICP-MS) [17]. In this paper, we report the results of our previous study, in which we increased the number of cases and cancer sites to improve the accuracy of our cancer risk estimation method for each cancer site (called the metallobalance (MB) method) and confirmed its reliability through follow-up surveys for practical application.

Materials and Methods

1. Case and Control Serum Samples

Case serum samples were collected from cancer patients who were hospitalized and treated at Kanagawa Prefectural Cancer Center and Chiba Prefectural Cancer Center during the 10-year period from April 2005 to March 2015. The cancer sites in the collected serum were six sites in men (stomach, colorectal, lung, liver, pancreas, prostate) and nine sites in women (stomach, colorectal, lung, liver, pancreas, breast, cervix, uterine body, ovary), which have high cancer incidence/mortality rates in Japan [3]. Patients were informed by their attending physicians about the provision of serum and other samples for medical research and the use of medical information for research, and provided written informed consent to participate in this study. After admission and examination, blood was collected from the cubital vein in the early morning in a fasting state, converted to serum, and stored at -80°C. A total of 2,912 serum samples was provided from cancer patients. The breakdown was 272 cases of stomach cancer (140 men, 132 women), 455 cases of colon cancer (271 men, 184 women), 427 cases of lung cancer (269 men, 158 women), 140 cases of liver cancer (110 men, 30 women), 277 cases of pancreas cancer (143 men, 134 women), 279 cases of prostate cancer, 461 cases of breast cancer (185 women), 295 cases of uterus cancer, and 121 cases of ovarian cancer.

The control group consisted of 5,814 individuals (2,181 men and 3,633 women) who underwent health checkups at 15 clinics in seven prefectures across Japan between April 2016 and March 2018, had no history of cancer, provided written consent to donate blood for this study. To confirm the diagnostic accuracy of the "cancer risk" prediction formula for six sites in men and nine sites in women derived from this case-control study, a total of 7,993 people (2,949 men and 5,044 women) who underwent this test over a two-year period from April 2019 to March 2021 at the same 15 facilities that cooperated in this study and gave written consent to a follow-up were surveyed by mail to confirm their cancer status within one year after the test. Confirmation of cancer status was confirmed by submitting a copy of the doctor's diagnosis certificate.

Blood samples (6 ml) from the control and follow-up groups were collected from a cubital vein in the morning at the clinic from participants who had skipped breakfast. After collection, the blood was left at room temperature for 60 minutes, then centrifuged at 3,000 rpm for 10 minutes. The serum was collected and stored in a refrigerator. A few days after collection, the collected serum was sent to the testing center by refrigerated delivery and stored at -80°C until trace element analysis was performed.

2. Study Design

In a previous report [17], we developed a diagnostic method for cancer risk. In this study, we conducted a new case-control study by increasing the number of subjects and cancer site. The study flow is shown in Figure 1. The case and control samples used in the analysis were randomly divided into two groups based on gender and cancer site, with one group serving as training data and the other as validation data. Discriminant analysis was performed on the training data, and based on the discriminant equations derived for gender and cancer site, the individual case and control data assigned to the validation data were substituted into each discriminant equation to verify their discriminant ability. After validation, the case and control data from the training and validation data were combined to increase the number of subjects, and a binomial logistic regression analysis was performed. We aimed to put the newly derived regression equation into practical use as a cancer risk estimation equation.

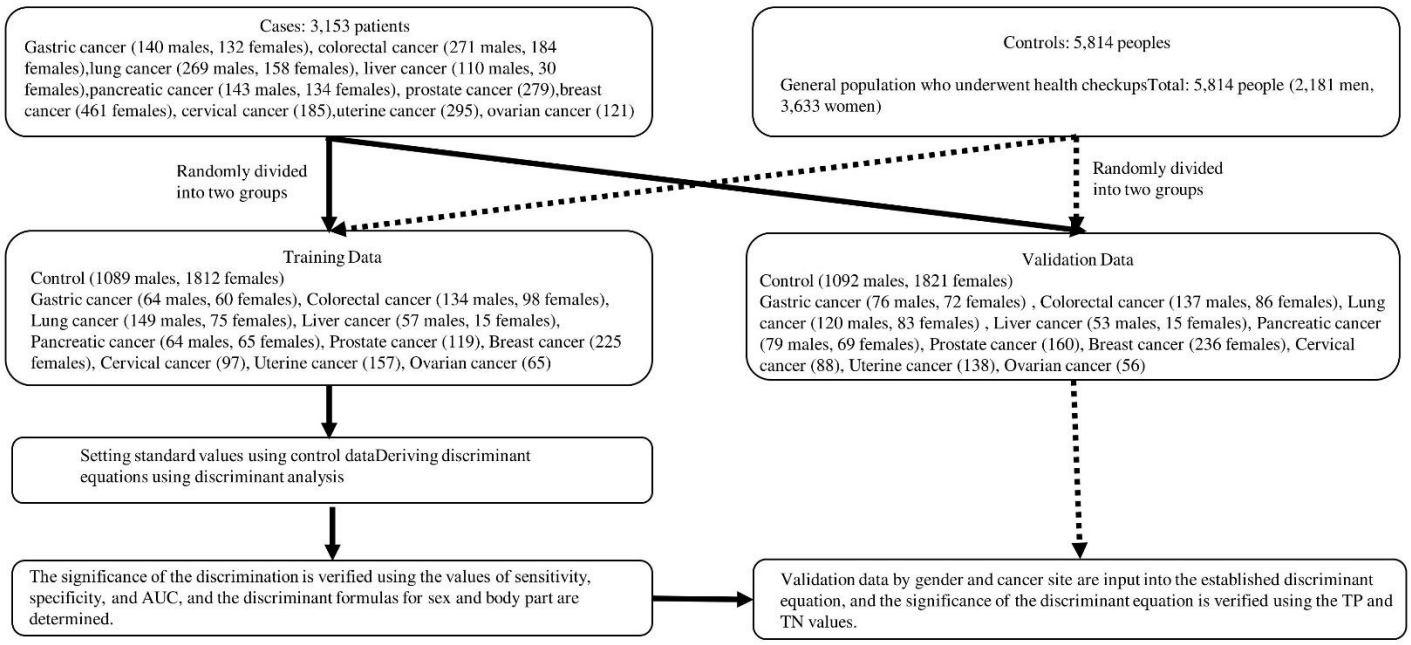

Figure 1: Case-Control Flow Two-Fold Cross-Validation

This MB test estimates cancer risk by categorizing the discriminant value calculated from the discriminant equation for each cancer site into four levels (A, B, C, D, with cancer risk increasing from A to D). The classification was determined using the discrimination value and sensitivity when the specificity was set to 80% for A and BCD, 95% for AB and CD, and 99% for ABC and D. By inputting the concentration data of 17 elements in the blood collected from new examinees into the cancer site-specific discrimination formula, it became possible to make an ABCD classification for six sites in men and nine sites in women.

3. Measurement and Analysis of Trace Element Concentrations

Trace element concentrations in serum were measured in a cleanroom using inductively coupled plasma mass spectrometry (ICP-MS) after nitric acid pretreatment. Based on the results of preliminary trials, 17 elements were selected for measurement (sodium (Na), magnesium (Mg), phosphorus (P), sulfur (S), potassium (K), calcium (Ca), iron (Fe), cobalt (Co), copper (Cu), zinc (Zn), arsenic (As), selenium (Se), rubidium (Rb), strontium (Sr), molybdenum (Mo), silver (Ag), and cesium (Cs)) whose measurements were stable and reproducible.

The validity of the discriminant equation obtained from the case-control study was evaluated using sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) [18,19]. The discriminant equation was validated by calculating the predictive value TP (true positive) in the case group and the predictive value TN (true negative) in the control group using validation data. Statistical analysis was performed using Excel Statistics (BellCurve, Japan) and SPSS Ver. 24 (IBM, USA).

4. Reagents and Measurement Methods

ICP-MS (Agilent 7800; Agilent Technologies, Santa Clara, CA, USA) was used for the measurement of trace elements. The reagents used for ICP-MS measurements were 61% nitric acid solution/30% hydrogen peroxide solution (Kanto Chemical, Tokyo, Japan), XSTC-622B (ICP-MS mixed standard solution; SPEX CertiPrep, Metuchen, NJ, USA), atomic absorption spectroscopy standard solutions (Na, Mg, P, S, K, Ca, Be, Te; Kanto Chemical, Tokyo, Japan), and ICP-MS metal standard solutions (Y, Rh; AccuStandard, Inc. New Haven, CT, USA). All containers used for the measurements (sample storage bottles, sample bottles, micropipette tips) were made of polypropylene to prevent leakage of trace elements. Furthermore, all containers were washed with ultrapure water (18.00 MΩ·cm or higher) and nitric acid to remove contamination from trace elements.

Results

Table 1 shows the number of serum samples used in the analysis by gender and age group. Table 2 shows the results of the discriminant analysis using the training data and the validation data. The discriminant analysis results showed that the sensitivity, specificity, and AUC for gastric cancer in men were 0.734, 0.907, and 0.901, respectively, and for gastric cancer in women were 0.783, 0.889, and 0.949, respectively. High sensitivity, specificity, and AUC were also obtained for other cancer sites. Furthermore, the accuracy of the discriminant equation was evaluated by calculating true positives (TP) and true negatives (TN) using the validation data. TP ranged from 0.7 to 0.85 for both men and women, and true negatives ranged from 0.8 to 0.95 for both men and women (Table 2).

Based on these results, a new binomial logistic regression analysis was performed using all data. The resulting ROC curves and AUCs (95% confidence intervals) are shown in Figure 2. Similar to the results of the discriminant analysis using the training data, the AUC was approximately 0.9 for both men and women for all cancer sites, demonstrating reliable discrimination results. Figure 3 compares the concentrations of the 17 measured elements by gender and cancer site in a radar chart. This chart shows the ratio, with the average value of the 17 elements in the control group taken as 1.0. Looking at all cancer sites, Co, Cu, As, Mo, and Ag tended to be high in both men and women, while Fe, Zn, Rb, and Cs tended to be low. Furthermore, even for elements with high or low values, differences in patterns were observed when looking at them by gender and cancer site.

Gender	Age-class	Control	Cancer case										
			Colorectal	Stomach	Lung	Liver	Pancreatic	Prostate	Brest	Cervical	Uterine	Ovarian	Total
Male	20-	78			1				-	-	-	-	1
	30-	243	5	1	5	2	2		-	-	-	-	15
	40-	530	24	4	8	9	11	1	-	-	-	-	57
	50-	477	64	27	40	21	22	29	-	-	-	-	203
	60-	496	105	50	77	95	63	115	-	-	-	-	505
	70-	329	69	47	109	103	43	125	-	-	-	-	496
	80-	28	4	11	29	35	2	9	-	-	-	-	90
	Total	2181	271	140	269	265	143	279	-	-	-	-	1367
Female	20-	178					1	-	4	5			10
	30-	448	3	4	2	2		-	61	20	8	8	108
	40-	895	11	11	8		7	-	119	51	47	22	276
	50-	962	41	15	22	5	23	-	43	39	96	36	320
	60-	767	73	40	59	31	49	-	150	32	93	35	562
	70-	364	53	47	55	58	44	-	70	25	44	18	414
	80-	18	3	15	11	19	10	-	14	11	7	2	92
	90-	1			1	1		-		2			4
	Total	3633	184	132	158	116	134	-	461	185	295	121	1786

Table 1: Number of controls and cancer patients by sex and age

Gender	Cancer sites	Training					Validation			
		No. of control	No. of case	sensitivity	specificity	AUC	No. of control	No. of case	True positive	True negative
Male	stomach	1,089	64	0.734	0.907	0.901	1,092	76	0.763	0.922
	colorectal		134	0.769	0.904	0.912		137	0.701	0.929
	lung		149	0.846	0.904	0.940		120	0.767	0.923
	liver		57	0.807	0.932	0.956		53	0.797	0.978
	pancreas		64	0.813	0.925	0.942		79	0.797	0.947
	prostate		119	0.798	0.841	0.892		160	0.688	0.851
Female	stomach	1,812	60	0.783	0.889	0.949	1,821	72	0.833	0.875
	colorectal		98	0.796	0.903	0.946		86	0.721	0.889
	lung		75	0.800	0.911	0.950		83	0.831	0.900
	liver		15	0.967	0.973	0.993		15	0.836	0.986
	pancreas		65	0.800	0.946	0.934		69	0.855	0.947
	breast		225	0.756	0.806	0.858		236	0.708	0.788
	cervix		97	0.742	0.859	0.872		88	0.750	0849
	uterine		157	0.783	0.880	0.915		138	0.717	0.874
	ovary		65	0.815	0.921	0.941		56	0.750	0.916

Table 2 Cross-validation results

Binary logistic regression analysis using training data yielded high sensitivity, specificity, and AUC values ranging from 0.742 to 0.956 for both men and women, and for all cancer sites. Validation data was then fed into these gender-specific and cancer-site-specific discriminant functions to calculate positive and negative predictive values, both of which also yielded high results.

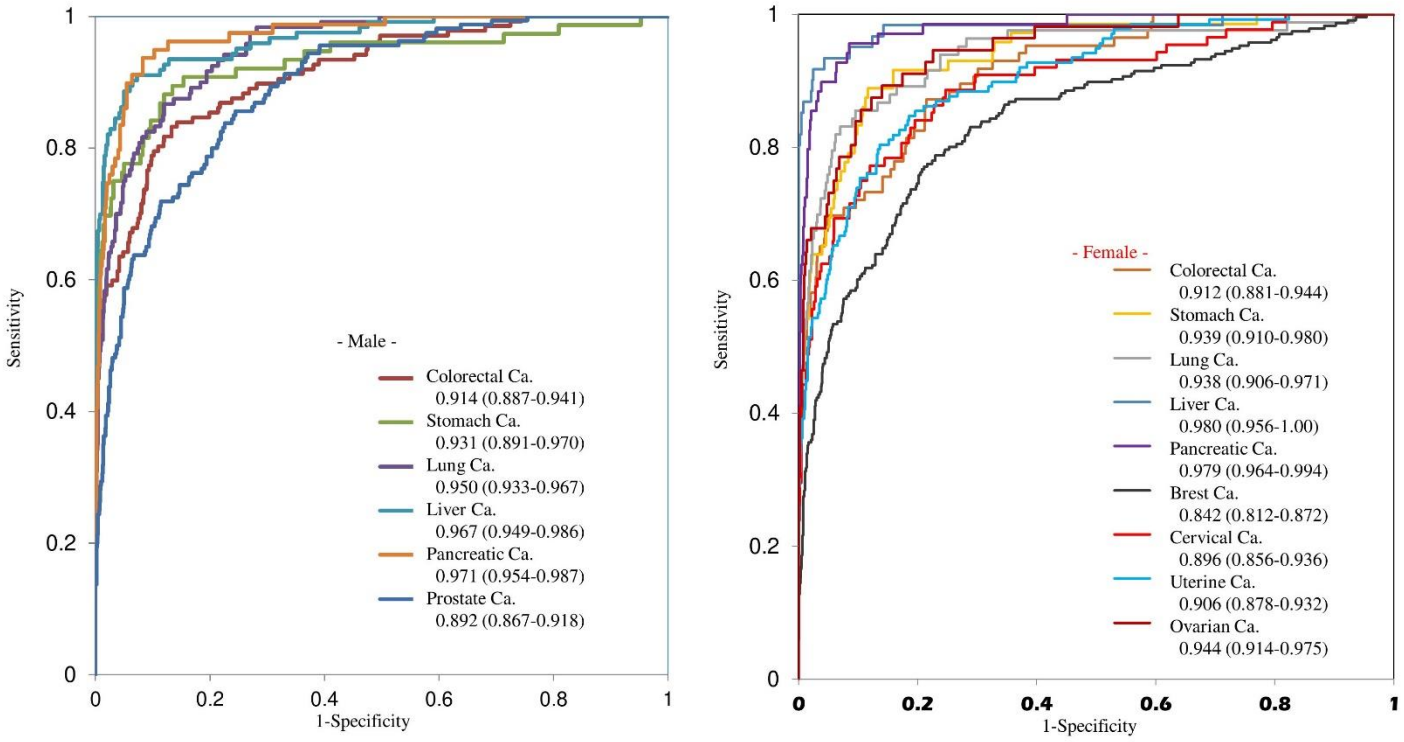

Figure 2: ROC curve and AUC from binary logistic regression analysis

The ROC curves are plotted according to the results of a binary logistic regression analysis performed using cases and controls, which combine the training and validation data. The left figure shows five cancer sites in men, and the right figure shows nine cancer sites in women. The numbers in the legend represent the AUC, and the numbers in parentheses represent the 95% confidence interval for the AUC..

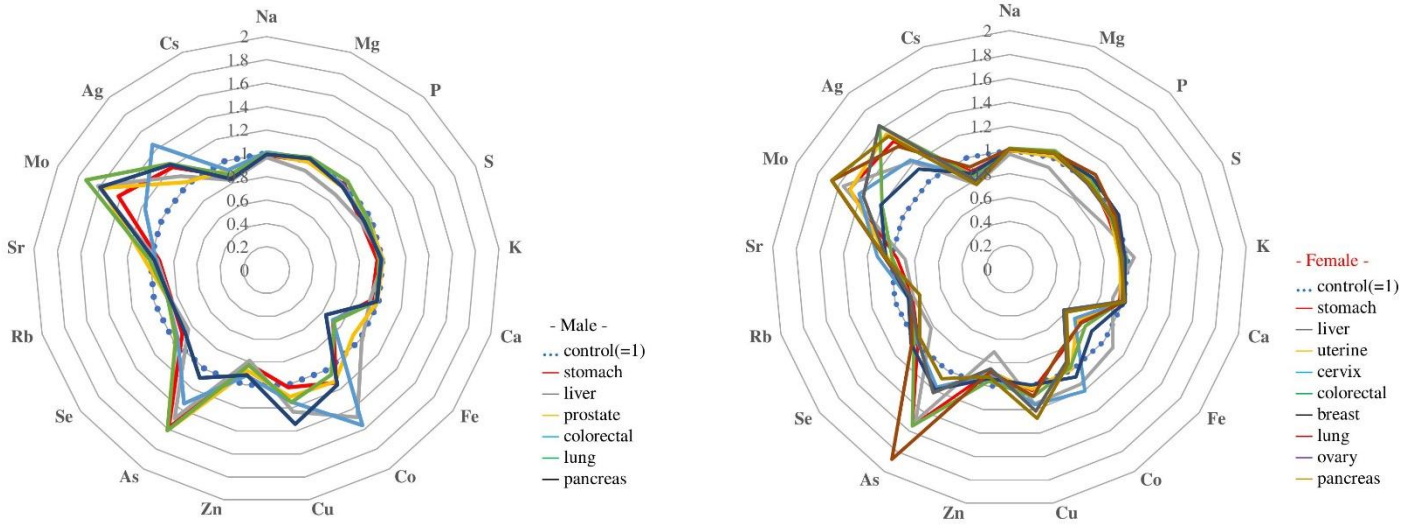

Figure 3: Comparison of elemental concentrations by cancer site (control=1)

The radar charts show the ratios of the average values of 17 elements measured by ICP-MS in six cancer sites in men (left figure) and nine cancer sites in women (right figure), with the control average set to 1.0. In both men and women, Co, Cu, As, Mo, and Ag were higher than the control, while Fe, Zn, Rb, and Cs were lower. However, the ratio patterns of the 17 elements differed in both men and women depending on the cancer site.

Table 3 shows the elements with significant regression coefficients in the regression equation derived from the binomial logistic regression analysis using all data. Elements rated as + or ++ (Mg, Co, Cu, Mo) are highly correlated with cancer risk, while elements rated as - or -- (S, Zn, Rb) are presumed to be factors that reduce cancer risk. Because these significant regression coefficients differed by gender and cancer site, we were able to create discriminant equations for each cancer site.

Elements	Male						Female								
	Colon	Stomach	lung	Liver	Pancreas	Prostate	Colon	stomach	Lung	Liver	Pancreas	Breast	Cervix	uterine body	ovaries
Na	++			--	--		++	-		--		+	+		
Mg	+	++	++		++	+	++	++	++		++	++	++	++	++
P		++	++						++			+			
S	--	--			--	--	--	--			--	+		--	--
K									--	++	--	--	--	--	--
Ca		--	--	--	++	++					++	++			++
Fe				++	-	+				+	-	-	-	--	--
Co	++	++		++		++	++					++	++		
Cu	++		++	++	++	++	++		++	++	++		++		++
Zn		--	--	--		--		--	--	--	--	--	--	--	-
As	++	+	+			++	++	+	++			++			
Se	++				--		+					++		+	
Rb	--				--	--	--	--	-	--	--	--			
Sr	-	--													
Mo		+	++	++	++	++	++	++	++	++	++	++	++	++	++
Ag	-						++							++	
Cs					--							--	-	-	--

Table 3: Significance of partial regression coefficients by gender and cancer site

The significance of the partial regression coefficients obtained from the final binary logistic regression analysis is shown. - and -- indicate a decrease in cancer risk at significance levels $P<0.05$ and $P<0.01$, respectively, while + and ++ similarly indicate an increase in cancer risk at significance levels $P<0.05$ and $P<0.01$.

To verify the accuracy and reliability of the MB test's ABCD assessment, a follow-up survey was conducted to confirm cancer onset one year after the date of examination. The cutoff value for cancer risk positivity was set at grade C or higher. The theoretical specificity was set at 95%. Among the 7,993 subjects in the follow-up survey (including those who underwent the test more than twice), the proportion of those diagnosed with CD was approximately 5%-10% depending on the cancer site. A mail-based follow-up survey was conducted for those diagnosed with a positive result, and approximately 70% responded. Table 4 shows the cancer onset status of the respondents by site. Taking male colorectal cancer as an example, the cutoff value for CD grade from the prediction formula yielded a specificity of 0.945, a sensitivity of 0.674, a false positive rate of 0.055, and a false negative rate of 0.326. Additionally, according to a Japanese government report, the annual incidence of colorectal cancer in men aged 20 to 79 is approximately 1 in 500. Therefore, of the 2,949 men who underwent the test, an estimated 5.9 (2,949/500) would have colorectal cancer and 2,943.1 would not. Based on this value, 3.98 (5.9 × 0.674) cancer patients would be classified as CD grade, and 161.87 (2,943.1 × 0.055) normal individuals would be classified as at high-risk group of cancer (CD grade). The theoretical positive predictive value of the CD grade would be 2.39% (3.98/ (3.98 + 161.87)). The actual positive predictive value of the follow-up survey was 0.8333 (2/240), less than 50% of the theoretical value, suggesting insufficient effectiveness. However, the predicted values for pancreatic cancer and prostate cancer in men exceeded the theoretical values, and those values for stomach cancer and colon cancer in women were shown to be almost equivalent to the theoretical values. It was also revealed that the positive predictive values for each site exceeded the incidence rate calculated from general population.

High-risk Cancer Site	Male					Female				
	No. of CD grade	No. of cancer	Positive predictive value (%)	Theoretical Predictive Value (%)	Incidence Rate (%)	No. of CD grade	No. of cancer	Positive predictive value (%)	Theoretical predictive value (%)	Incidence Rate (%)
Gastric Ca.	193	2	1.0363	1.5404	0.1250	424	2	0.4717	0.4995	0.0476
Colorectal Ca.	240	2	0.8333	2.3900	0.2000	448	7	1.5625	1.6320	0.1111
Lung Ca.	256	1	0.3906	1.1494	0.1250	251	0	-	0.8598	0.0588
Pancreatic Ca.	257	1	0.3891	0.3359	0.0333	214	0	-	0.5635	0.0244
Prostate Ca.	271	4	1.4760	0.8038	0.1429	-	-	-	-	
Breast Ca.	-	-	-	-		402	2	0.4975	1.0352	0.2000
Uterine Ca.	-	-	-	-		238	1	0.4202	1.0048	0.0714

Table 4. Results of a follow-up survey on cancer incidence one year after MB testing for those diagnosed with CD grade between April 2019 and March 2021

This table shows the results of a cancer incidence survey conducted within one year of testing for individuals diagnosed with CD in MB testing. The incidence rates in the table represent the average for Japanese individuals aged 20 to 79 in 2009. Based on this rate, the theoretically predictable cancer incidence rate for individuals diagnosed with CD was calculated, and the table also shows the rate at which cancer was actually confirmed (positive predictive value) from follow-up surveys of individuals diagnosed with CD.

Discussion

It is estimated that one in two Japanese people will develop cancer and one in three will die from it [20]. Cancer control is an urgent issue in Japan, as it is in other developed countries around the world. The introduction of cancer screening for early detection and treatment is an important policy goal [21]. In particular, methods using bodily fluids such as blood, urine, and saliva are currently being developed because they are easy to administer and less burdensome to patients. Currently, tumor markers (e.g., CA125, CA19-9, CEA, SCC), PSA for prostate cancer, ABC screening for gastric cancer, and urinary NMP22 and CK8-18 for bladder cancer are being measured. However, due to insufficient accuracy, new cancer screening methods are being actively developed that measure microRNAs [22], nucleosomes [23], amino acids [24], and polyamines in blood, urine, and saliva [25]. In particular, in recent years, research has been conducted on the Multiple Cancer Early Detection (MCED) approach, which explores the possibility of identifying cancer sites through detailed examination of microRNAs in blood and urine [26,27,28]. This "cancer risk diagnostic method" using microRNAs in blood, urine, and saliva has been reported to demonstrate high sensitivity and specificity. However, although this MCED approach has high specificity, it has low sensitivity and is difficult to identify the location of cancer, so it is thought that its introduction as a cancer screening method is premature [29].

We have been working on developing a new "cancer risk" screening method using a stable trace element measurement method using ICP-MS. Of the 17 elements measured in this study, significant differences in concentrations were observed for many elements between the case and control groups. However, it is difficult to determine cancer risk by site based on individual elements alone. However, by creating discriminant equations for each cancer site using multivariate analysis, it became possible to calculate risk estimates for each site. Several studies have been published on the relationship between blood trace elements and cancer. Nakayama et al. [30] compared serum metallothionein, copper, and zinc levels in patients with chronic hepatitis, liver cirrhosis, and liver cancer, and reported that classification was possible with 80-90% sensitivity for each. Wu et al. [31] examined 13 elements in the serum of 25 breast cancer patients, 43 benign breast cancer patients, and 26 healthy individuals. They reported that Co, Ni, and Al were significantly higher in breast cancer patients, and logistic regression analysis revealed significantly higher levels of Cd, Mn, Fe, Cr, and Zn, enabling discrimination with a sensitivity of over 96%. Yasuda et al. [32] performed logistic regression analysis using 24 elements in hair samples from 124 solid cancer patients and 86 healthy individuals, reporting an AUC of 0.918 and significant results for I, As, Zn, Fe, Na, Se, K, and Mn. These findings, combined with the results of this study, indicate that cancer risk can be predicted based on differences in the balance of trace element concentrations in the blood. In this study, we improved the accuracy and reliability of the results by adding new case and control data to the data used in our previous report [17], resulting in a more reliable and accurate cancer risk screening method (MB test). As a result, the sensitivity, specificity, and AUC values of this MB test were high for all cancer sites. Furthermore, the positive predictive value calculated based on a one-year cancer incidence survey of high-risk participants was close to the theoretically calculated predictive value, and this value was 2 to 10 times the general incidence rate, indicating that this MB test is effective in diagnosing "cancer risk."

However, when elements like zinc exhibit diurnal fluctuations [33], many problems remain to be solved, including the presence of elements unsuitable for ICP-MS analysis (e.g., Mn, Ti, Sn), the presence of elements suspended in the atmosphere (e.g., Al) [34], differences in blood elemental concentrations based on age, place of residence, and race, and the timing of blood collection and storage/transportation methods [35]. Furthermore, there are very few reports on the mechanisms of interaction between multiple elements or the relationship between changes in elemental concentration balance and disease. Progress in these areas of research is eagerly awaited.

Conclusion

The MB test, a new "cancer risk diagnostic method" described in this report, has significant advantages: it does not require low-temperature storage, is less expensive than tests measuring proteins or RNA, and can estimate the risk of multiple cancer sites at once with a single annual blood sample. Therefore, it is appropriate to position it as a form of pre-cancer screening. This test will motivate people judged to be at high risk

of cancer to actively and continuously undergo cancer screenings and health checkups, contributing to cancer prevention for many people.

Conflict of Interest

The authors are affiliated with Renatech Co., Ltd., and some of their research results are patented. They also receive part of the research funding from Renatech, but this does not affect the results of this study.

Acknowledgments

Part of this research was supported by the Ministry of Economy, Trade and Industry's "Strategic Fundamental Technology Advancement Support Project" (No. 2831412036) for fiscal years 2016-2018, and was conducted as a collaborative project between Chiba Cancer Center, Kanagawa Cancer Center, and Renatech Co., Ltd. We would like to express our gratitude to the late Dr. Haruo Mikami and Dr. Hiroki Nagase of the Chiba Cancer Center and Dr. Yohei Miyagi of the Kanagawa Cancer Center for their generous cooperation in this research, as well as to all those involved at 15 clinics) in seven prefectures in Japan.

References

1. Kyle J.G., Guojun L., (2020). An Overview of Cancer Prevention: Chemoprevention and Immunoprevention. J Cancer Prev, 25(3), 127-135.
2. Akaza H., Tsuruo T., Saijo N., Sone S., Isonishi., Ohashi Y., et al., (2005). Cancer screening. Gan To Kagaku Ryoho, 32(1), 125-134.
3. Cancer Statistics Japan Editorial Board., (2009). International Comparisons of Cancer Mortality and Cancer Screening Rates. Cancer Statistics Japan, 21. Foundation for Promotion of Cancer Research.
4. Takeda E., Katsuyama Y., Sogai D., Yu L., Kumagae Y., Yokokawa D., et al., (2023). Cancer Screening Abstinence Rates and Rationales Among Regular Outpatients at a Rural Hospital in Japan: A Cross-Sectional Study. Int J Gen Med, 16, 5235-5240.
5. Poulet G., Massias J., & Taly V., (2019). Liquid Biopsy: General Concepts. Acta Cytol, 63(6), 449-455.
6. Spivak J. L., (2002). Iron and the anemia of chronic disease. Oncology, 16(9), 25-33.
7. Emsrud K. E., Duong T., Cauley J. A., Heaney R. P., Wolf R. L., et al., (2000). Low fractional calcium absorption increases the risk for hip fracture in women with low calcium: Study of Osteoporotic Fractures Research Group. Ann Interm Med, 132(5), 345-353.
8. Saito M., Osono T., Watanabe J., Yamamoto T., Takeuchi M., Ohyagi Y., & Katsunuma H. (1961). Studies on Minamata disease. I. Establishment of the criterion for etiological research in mice. Jpn J Exp Med. Aug;31, 277-290.
9. Chen J., (2012). An original discovery: selenium deficiency and Keshan disease (an endemic heart disease). Asia Pac J Clin Nutr, 21(3), 320-326.
10. Cal L., Chen T., Yang J., Zhou K., Yan X., et al. (2015). Serum trace element differences between Schizophrenia patients and controls in the Han Chinese population. Scientific Reports 5, 15013.
11. Lutsey P. L., Alomso A., Michos E. D., Loehr L. R., Astor B., et al., (2014). Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. Am J Cin Nutr, 100(3), 756-764.
12. Pavithra V., Sathisha T. G., Kasturi K., Mallika D. S., Amos S. J., et al., (2015). Serum Levels of Metal Ions in Female Patients with Breast Cancer, J Clinic and Diag Research, 9(1), BC25-c27.
13. Gupta S. K., Shukla V. K., Vaidya M. P., Roy S. K., & Gupta S., (1991). Serum trace elements and Cu/Zn ratio in breast cancer patients. J Surg Oncol, 46(3), 178-181.
14. Gal D., Lischinsky S., Friedman M., & Zinder O., (1989). Prediction of the presence of ovarian cancer at surgery by an immunochemical panel: CA125 and zinc ratio. Gynecol Oncol, 35(2), 246-250.
15. Pirinççi N., Geçit I., Gunes M., Kaba M., Tanik S., et al., (2013). Levels of Serum Trace Elements in Renal Cell Carcinoma Cases, Asian Pacific J Cancer Prev, 14(1), 499-502.
16. Diez M., Arroyo M., Cerdan F. J., Munoz M., Martin M. A., et al., (1989). Serum and tissue tarce metal levels in lung cancer. Oncology, 46(4), 230-234.
17. Okamoto N., Mikami H., Nakamura Y., Kusakabe M., Yamamoto N., et al., (2020). A Nobel Multivariate Index for Cancer Risk Detection Based on the Serum Trace Elements: Metallo-Balance Method. J Cancer Epidemiology & Prevention, 5(1), 1-8.
18. Hanley J. A., & McNeil B. J., (1982). The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology, 143(1), 29-36.
19. Hajian-Tilaki K., (2013). Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. Caspian J Intern Med, 4(2), 627-635.
20. Foundation for Promotion Cancer Research (edited)., (2025). Cumulative Cancer Incidence/Mortality Risk. Cancer Statistics in Japan, 34-35.
21. Hashimoto T., & Takahashi H., (2024). Cancer screening programs in Japan: Progress and challenges. J Med Screen, 31(4), 207-210.
22. Shimomura A., Shiino S., Kawauchi J., Takizawa S., Sakamoto H., et al., (2016). Novel combination of serum microRNA for detecting breast cancer in the early stage. Cancer science, 107(3), 326-334
23. Ito H., Hasegawa K., Hasegawa Y., Nishimaki T., Hosomichi K., et al., (2015). Silver Nanoscale Hexagonal Column Chips for Detecting Cell-free DNA and Circulating Nucleosomes in Cancer Patients. Sci Rep, 5, 10455.
24. Miyagi Y., Higashiyama M., Gochi A., Akaike M., Miura T., et al., (2011). Plasma free amino acid profiling of five types of cancer patients and its application for early detection. PLoS One, 6(9), e24143.
25. Takayama T., Tsutsui H., Shimizu I., Toyama T., Yoshimoto N., et al., (2016). Diagnostic approach to breast cancer patients based on target metabolomics in saliva by liquid chromatography with tandem mass spectrometry. Clin Chim Acta, 452, 18-26.
26. Klein E. A., Richards D., Cohn A., Tummala M., Lapham R., Cosgrove D., et al., (2021). Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. Ann Oncl, 32(9), 1167-1177.
27. Matsuzaki J., Kato K., Ono K., Tsuchiya N., Sudo K., et al.,

(2023). Prediction of tissue-of-origin of early-stage cancers using serum miRNomes. JNCI Cancer Spectrum, 7(1), pkac080.

28. Baba S., Kawasaki T., Hirano S., Nakamura T., Asano T., et al., (2024). A noninvasive urinary microRNA-based assay for the detection of pancreatic cancer from early to late stages: a case control study. EClinicalMedicine, 78, 102936.
29. Wade R., Nevitt S., Liu Y., Harden M., Khouja C., et al., (2025). Multi-cancer early detection tests for general population screening: a systematic literature review. Health Technol Assess. 29(2), 1-105.
30. Nakayama A., Fukuda H., Ebara M., Hamasaki H., Nakajima K., et al., (2002). A new diagnostic method for chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma based on serum metallothionein, copper, and zinc levels. Biol Pharm Bull. 25(4), 426-431.
31. Wu H. D., Chou S. Y., Chen D. R., Kup H. W., (2006). Differentiation of serum levels of trace elements in normal and malignant breast patients. Biol Trace Elem Res. 113(1), 9-18.
32. Yasuda H., Yoshida K., Segawa M., Tokuda R., Tsutsui T., et al., (2009). Metallomics study using hair mineral analysis and multiple logistic regression analysis: relationship between cancer and minerals. Environ Health Prev Med. 14(5), 261-266.
33. Markowitz M. E., Rosen J. F., & Mizruchi M., (1985). Circadian variations in serum zinc (Zn) concentrations: correlation with blood ionized calcium, serum total calcium and phosphate in humans. American Journal of Clinical Nutrition, 41(4), 689-696.
34. May T. W., & Wiedmeyer R. H. (1998). A table of polyatomic interferences in ICP-MS. Atomic Spectroscopy, 19(5), 150-155.
35. Simić A., Hansen A. F., Syversen T., Lierhagen S., Ciesielski T. M., Romundstad P. R., et al., (2022). Trace elements in whole blood in the general population in Trøndelag County, Norway: The HUNT3 Survey. Sci Total Environ, 806(Pt 4), 150875.

DOI:10.31579/2690-4861/1072