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## PREDICTIVE VALUE OF SERUM TRACE ELEMENTS FOR CHEMOTHERAPEUTIC EFFICACY IN GASTRIC AND COLON CANCER: A CROSS-SECTIONAL STUDY

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### ABSTRACT

**Introduction:** Colorectal cancer remains a leading cause of cancer mortality worldwide, characterized by significant heterogeneity in therapeutic response. Essential trace elements, serve as critical cofactors in DNA repair mechanisms, apoptotic signaling, and drug transport. This study aimed to evaluate the predictive value of baseline serum levels of these elements regarding the clinical response to first-line chemotherapy in patients with colon cancer.

**Material and Methods:** This descriptive-analytical cross-sectional study was conducted at Imam Khomeini Hospital, Urmia University of Medical Sciences, Iran. A total of 30 patients with histologically confirmed colon cancer receiving standard platinum-based chemotherapy were enrolled. Pre-treatment serum concentrations of Zn, Cu, and Mg were quantified using colorimetric assays. Treatment response was evaluated upon completion of the regimen according to RECIST criteria. Associations between trace element levels and chemotherapy response (Complete Response vs. Non-Response) were analyzed using independent t-tests and multivariate logistic regression.

**Results:** The cohort exhibited a mean age of  $60.31 \pm 10.61$  years and a distinct female predominance (63.3 %). A high rate of therapeutic resistance was observed, with 56.7 % of patients classified as non-responders. Patients achieving a Complete Response demonstrated significantly higher baseline serum Magnesium levels ( $2.07 \pm 0.22$  mg/dL) compared to non-responders ( $1.83 \pm 0.36$  mg/dL;  $P=0.047$ ). Multivariate logistic regression identified serum Magnesium as a significant independent predictor, where higher levels reduced the likelihood of non-response ( $P=0.048$ ). Serum Zinc and Copper levels did not show statistically significant associations with treatment outcomes in this cohort ( $P>0.05$ ).

**Conclusion:** Baseline serum Magnesium levels are significantly associated with chemotherapy efficacy in colon cancer patients. These findings suggest that adequate magnesium status may facilitate optimal pharmacodynamic activity, potentially by modulating the cellular uptake of platinum-based agents. Routine assessment of serum Magnesium could serve as an accessible biomarker for stratifying patients at risk of chemoresistance.

**KEYWORDS:** Colon Cancer, Magnesium, Trace Elements, Chemotherapy Response, Biomarkers

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## INTRODUCTION

Gastrointestinal malignancies, specifically gastric and colorectal cancers, constitute a substantial proportion of the global oncological burden, ranking among the leading causes of cancer-related mortality worldwide [Singh A. 2024]. Despite significant advancements in surgical techniques and the advent of targeted immunotherapies, systemic chemotherapy remains the cornerstone of treatment for advanced and metastatic stages [Leng G et al. 2024]. Standard regimens, typically relying on the synergistic cytotoxicity of fluoropyrimidines combined with platinum-based agents (such as oxaliplatin or cisplatin), have improved survival outcomes [Fong C. 2016]. However, the clinical management of these patients is frequently confounded by significant heterogeneity in therapeutic response [Gewandter J et al. 2019]. A considerable subset of patients exhibits primary de novo resistance or develops secondary resistance, leading to treatment failure and unnecessary exposure to severe toxicities [Lei Z et al 2020]. Consequently, the identification of accessible, cost-effective, and reliable predictive biomarkers is imperative to stratify patients and optimize pharmacotherapeutic strategies [Passaro A et al. 2024].

Emerging research has increasingly highlighted the pivotal role of essential trace elements in modulating oncogenesis and therapeutic sensitivity [Górska A et al 2024]. Zinc (Zn), Copper (Cu), and Magnesium (Mg) transcend their roles as simple micronutrients to function as obligatory cofactors for metalloenzymes involved in DNA replication, apoptotic signaling, and oxidative stress regulation, thereby exerting a profound influence on tumor physiology and drug pharmacodynamics [Wong C et al 2025]. Specifically, Zinc is indispensable for maintaining genomic fidelity and facilitating p53-dependent apoptosis [Puca R et al. 2011]. As a structural component of the tumor suppressor protein p53 and a cofactor for the antioxidant enzyme superoxide dismutase (SOD), Zinc is essential for the execution of cell death pathways triggered by cytotoxic agents [Akhtar M et al 2012]. In contrast, Copper is a key driver of neovascularization and metastatic spread [Kamiya T. 2022]; elevated serum concentrations frequently correlate with disease progression, suggesting that the copper-to-zinc ratio may possess significant

prognostic utility [Ullah M et al. 2025]. Furthermore, Magnesium is critical for the function of DNA repair enzymes and has been identified as a determinant of the cellular influx and cytotoxicity of platinum-based chemotherapeutics [Ma Y et al. 2025]. Consequently, systemic dysregulation of these ionic homeostatic mechanisms may critically compromise the efficacy of antineoplastic regimens [Zhou S et al 2024].

Despite the established mechanistic links between these trace elements, cellular survival pathways, and drug transport, clinical data correlating baseline serum levels with chemotherapy outcomes in gastrointestinal malignancies remain fragmented [Rafieemehr H et al 2024]. Few studies have simultaneously evaluated these three elements across both gastric and colon cancer cohorts to determine their predictive utility [Arianmanesh F et al 2025]. This study aims to bridge this gap by investigating the association between pre-treatment serum concentrations of Zinc, Copper, and Magnesium and the clinical response to first-line chemotherapy in patients with gastric and colon cancer.

## MATERIALS AND METHODS

**Study Design and Setting:** This descriptive-analytical cross-sectional study was conducted at the Department of Oncology, Imam Khomeini Hospital, affiliated with Urmia University of Medical Sciences, Urmia, Iran. The study protocol was designed to evaluate the correlation between serum trace element levels and chemotherapy response in patients with gastrointestinal malignancies.

**Study Population:** The study population comprised patients with a histologically confirmed diagnosis of gastric or colorectal cancer who were referred to the oncology center.

- **Inclusion Criteria:** Patients were eligible if they were between 18 and 65 years of age, were newly diagnosed, and were candidates for first-line chemotherapy.
- **Exclusion Criteria:** Patients were excluded if they had received any prior therapeutic interventions (chemotherapy, radiotherapy, or surgery) for the current malignancy; had a history of malignancies other than those of the gastrointestinal tract; or had a history of chronic intestinal diseases (e.g., inflammatory bowel disease or malabsorption syndromes).

**TABLE 1**  
Demographic and Clinical Characteristics  
of Patients with Colon Cancer (n=30)

Characteristic	Category / Statistic	Value
Age (years)		60.31 ± 10.61
BMI (kg/m <sup>2</sup> )		24.08 ± 2.79
Gender	Male	11 (36.7%)
	Female	19 (63.3%)
Tumor Stage (T)	T0	9(30.0%)
	T1	3 (10.0%)
	T2	12(40.0%)
	T3	5 (16.7%)
	T4	1 (3.3%)
Disease Recurrence	No	13 (43.3%)
	Yes	17(56.7%)
Response to Treatment	Complete Response	13(43.3%)
	Non-Response	17(56.7%)

**Sample Collection and Biochemical Analysis:** Demographic and clinical data, including age, gender, Body Mass Index (BMI), tumor stage (TNM classification: T0-T4), and disease recurrence status, were extracted from medical records and recorded in a structured checklist (Table 1).

For biochemical analysis, peripheral venous blood samples (5 mL) were collected from all participants prior to the initiation of the first chemotherapy cycle. Sampling was performed by trained laboratory personnel following a minimum 12-hour overnight fast to minimize postprandial variations. Blood was drawn into vacuum tubes containing a gel separator (clot activator).

The samples were allowed to clot at room temperature for 20 minutes. Subsequently, serum was separated by centrifugation at 3000 rpm for 10 minutes. The separated serum was aliquoted into 1.5 mL microcentrifuge tubes and stored at -80°C until batch analysis to ensure sample stability.

Serum concentrations of zinc (Zn), copper (Cu), and magnesium (Mg) were measured using inductively coupled plasma mass spectrometry (ICP-MS), following standardized protocols for trace element analysis. They were quantified using commercially available colorimetric assay kits (Dialab, Austria). Internal standards and calibration curves were applied to minimize matrix effects and instrument drift. The analysis was performed using an automated clinical chemistry analyzer (Biotechnica Instruments, Model BT1500, Italy) according to the manufacturer's instructions.

**Chemotherapy Regimen:** Patients received standard first-line chemotherapy for colon cancer (e.g., fluoropyrimidine plus platinum-based regimen) according to institutional protocols. Dose modifications were documented.

**Assessment of Treatment Response:** The primary clinical outcome was the response to chemotherapy, evaluated by a senior medical oncologist upon completion of the treatment course. Patients were categorized into three groups based on clinical and radiological assessment:

1. Complete Response: Disappearance of all target lesions.
2. Partial Response: Significant reduction in tumor burden.
3. Non-Response: Including stable disease or progressive disease.

**Ethical Considerations:** The study protocol was reviewed and approved by the Ethics Committee of Imam Khomeini Hospital, Urmia University of Medical Sciences (Approval ID: IR.UMSU.HI-MAM.REC.1402.107). All procedures were conducted in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki.

**Sample Size Determination and Sampling Method:** The minimum required sample size was calculated based on the mean and standard deviation (SD) of serum zinc levels reported in a reference study on colon cancer patients by Wu et al. (2020) (Mean ± SD: 856 ± 322.5 ug/L). Using the standard formula for estimating a population mean, with a 95% confidence interval (Z, 1-0.5α = 1.96) and a desired precision (d) set at 20% of the standard deviation (0.2 SD), the study required a minimum of 60 patients.

$$n = \frac{Z_{1-0.5\alpha}^2 \times S^2}{d^2}$$

Participants were recruited using a convenience sampling method.

**Statistical Analysis:** Data were analyzed using IBM SPSS Statistics software, version 26.0. Quantitative variables are reported as mean ± standard deviation (SD), and qualitative variables are presented as frequencies and percentages (n, %).

➤ The Independent Student's t-test (or Mann-Whitney U test for non-normally distributed data) was used to compare mean serum levels

and continuous demographic variables between response groups.

- The Chi-square test was utilized to compare categorical variables.
- Binary Logistic Regression was employed to determine the association between serum trace element levels and the likelihood of chemotherapy response.
- A P-value of <0.05 was considered statistically significant.

**RESULTS**

**Demographic and Clinical Characteristics of Colon Cancer Patients:** A total of 30 patients with colon cancer were included in the final analysis. The cohort had a mean age of  $60.31 \pm 10.61$  years and a mean BMI of  $24.08 \pm 2.79$  kg/m<sup>2</sup>. In contrast to the gastric cancer group, the colon cancer cohort exhibited a female predominance, comprising 63.3% females (n=19) and 36.7% males (n=11).

Regarding tumor pathology, the most frequent stage at diagnosis was T2 (n=12, 40.0%), followed by T0 (n=9, 30.0%), T3 (n=5, 16.7%), T1 (n=3, 10.0%), and T4 (n=1, 3.3%). Disease recurrence was documented in 56.7% (n=17) of the patients. Regarding the primary clinical outcome, 43.3% of patients (n=13) achieved a Complete Response to chemotherapy, while 56.7% (n=17) were classified as Non-Responders. No patients in this specific cohort were classified as having a partial response.

**Serum Trace Element Levels:** The baseline mean serum concentrations for the colon cancer cohort were:

- **Magnesium (Mg):**  $1.93 \pm 0.32$  mg/dL
- **Zinc (Zn):**  $91.13 \pm 25.28$  ug/dL
- **Copper (Cu):**  $130.40 \pm 21.51$  ug/dL

When compared to gastric cancer patients (as per the full dataset analysis), colon cancer patients exhibited significantly lower mean serum Magnesium levels (P=0.05) and significantly higher mean serum Copper levels (P=0.02).

**Association between Serum Trace Elements and Chemotherapy Response:** Patients were stratified into “Complete Response” and “Non-Response” groups to evaluate the predictive value of baseline trace elements (Table 2).

A statistically significant association was observed for Magnesium. Patients who achieved a Complete

**TABLE 2.**

Comparison of Baseline Serum Trace Element Levels Between Responders and Non-Responders in Colon Cancer

Trace Element	Complete Response (n=13)	Non-Response (n=17)	P-value
Magnesium (mg/dL)	2.07±0.22	1.83±0.36	0.047*
Zinc (ug/dL)	98.92±23.89	85.17±25.36	0.143
Copper (ug/dL)	124.07±17.16	135.23±23.66	0.163

**NOTES:** (\*) - Values are presented as Mean ± Standard Deviation. Based on Independent Student's t-test. Statistically significant (P < 0.05).

Response had significantly higher baseline serum Magnesium levels ( $2.07 \pm 0.22$  mg/dL) compared to Non-Responders ( $1.83 \pm 0.36$  mg/dL; P=0.047).

Mean serum Zinc levels were higher in the complete response group ( $98.92 \pm 23.89$  ug/dL) compared to the non-response group ( $85.17 \pm 25.36$  ug/dL), but this difference did not reach statistical significance (P=0.143).

Serum Copper levels were lower in responders ( $124.07 \pm 17.16$  ug/dL) compared to non-responders ( $135.23 \pm 23.66$  ug/dL), but the difference was not statistically significant (P=0.163).

**Predictors of Treatment Non-Response:** Multivariate logistic regression analysis was conducted to identify independent predictors of chemotherapy non-response (Table 3).

Serum Magnesium emerged as a significant predictor. The analysis revealed a significant inverse association (Odds Ratio [OR]: 0.034; 95% CI: 0.001 – 0.971; P=0.048), indicating that higher baseline Magnesium levels significantly reduced the likelihood of non-response (i.e., increased the odds of achieving a response).

Neither serum Zinc (P=0.119) nor Serum Cop-

**TABLE 3.**

Multivariate logistic regression analysis predicting non-Response to Chemotherapy in Colon Cancer Patients

Variable	Odds Ratio	95% Confidence Interval (CI)	P-value
Serum magnesium (ug/L)	0.034	0.001–0.971	0.048*
Serum zinc (ug/L)	0.970	0.939–1.007	0.119
Serum copper (ug/L)	1.024	0.982–1.069	0.262

**NOTES:** Dependent variable: Non-Response to treatment (Reference category: Complete Response). Odds Ratio greater than 1 indicates that higher levels reduce the risk of non-response.

per ( $P=0.262$ ) showed a statistically significant predictive value for treatment outcome in the regression model, although trends followed the univariate analysis (Zinc: inverse association, Copper: direct association with non-response).

### DISCUSSION

Oncogenesis and therapeutic resistance are fundamentally driven by the diverse molecular landscape of the tumor microenvironment, encompassing both genomic instability and non-genetic variations [Hassan M et al 2024]. Consequently, scientific inquiry has increasingly focused on the metallome, specifically zinc, copper, and magnesium, as these ions serve as obligate cofactors for the enzymatic machinery responsible for resolving DNA damage and mitigating oxidative stress [Amhare A et al 2025]. The present study investigated the prognostic utility of baseline serum trace elements, Magnesium, Zinc, and Copper, in predicting the clinical response to first-line chemotherapy in patients with colon cancer. The most salient finding of this investigation was the independent and statistically significant association between higher baseline serum Magnesium levels and the achievement of a Complete Response. While serum Zinc and Copper levels exhibited trends consistent with their established biological roles (higher Zinc and lower Copper in responders), these associations did not reach statistical significance in this specific cohort.

The demographic characterization of the colon cancer cohort indicated a mean age at diagnosis of approximately 60 years, a figure markedly lower than the median of 68–72 years typically documented in Western industrial regions, including the United States and Western Europe [Siegel R et al 2024]. Corroborating this trend, AziziKia and co-authors. and data from the Iranian National Cancer Registry [Rahimi F et al 2024; AziziKia H et al. 2025] have consistently localized the peak incidence to the fifth and sixth decades of life. This epidemiological distinctiveness is frequently ascribed to a ‘nutritional transition’, characterized by the accelerated adoption of Western dietary patterns rich in processed meats and refined carbohydrates, superimposed upon a population pyramid that is structurally younger than that of Europe [Arnold M et al 2017].

Moreover, the cohort displayed a marked pre-

ponderance of female patients, a demographic profile that diverges from the male bias typically observed in global colorectal cancer statistics [White A et al 2018]. This inversion of the gender ratio may be ascribed to the anatomical predilection of tumors; females demonstrate a documented susceptibility to proximal (right-sided) colon malignancies, which are characterized by distinct molecular phenotypes and are frequently diagnosed at advanced stages relative to distal lesions [Kim S et al 2015]. Consequently, an enrichment of right-sided pathologies within this specific catchment area would plausibly account for both the observed female skew and the elevated rates of therapeutic resistance [Majek O et al. 2013]. Although our data stands in contrast to the male dominance reported generally in Iranian patients by AziziKia et al. [AziziKia H et al. 2025], it resonates with sub-group analyses by Majek et al., who identified that the typical male advantage is attenuated or reversed in older age groups and specifically within proximal subsites [Majek O et al. 2013].

The observed recurrence and non-response rates of 56.7% underscore a clinically aggressive phenotype within this cohort, exceeding resistance levels typically reported in pivotal phase III trials for metastatic disease, where objective response rates generally range from 40% to 50% [Biller L, Schrag D. 2021]. This high rate of therapeutic failure, despite a prevalence of early anatomical staging (T0-T2), suggests a discordance between tumor burden and biological behavior, likely attributable to occult micrometastases or intrinsic molecular resistance mechanisms as described by Lawrence et al. [Lawrence R et al 2023]. Furthermore, this refractory profile may reflect regional epidemiological distinctiveness, specifically the “right-sided shift” and younger age of onset frequently documented in Middle Eastern populations [Ghasemi-Kebria F et al. 2004]; right-sided malignancies are embryologically distinct and historically less responsive to standard adjuvant chemotherapy [Kurniali P et al 2010]. Collectively, these findings expose the inadequacy of TNM staging alone in predicting chemosensitivity and validate the urgent necessity for integrating accessible biomarkers, such as serum magnesium, to stratify patients and mitigate the risks of futile cytotoxic exposure [Biller L, Schrag D. 2021].

The standout finding of this study is the significant predictive value of serum Magnesium. Patients with higher baseline magnesium levels had drastically reduced odds of non-response. This aligns with a growing body of evidence suggesting that magnesium homeostasis is critical for the efficacy of platinum-based chemotherapies (e.g., oxaliplatin) commonly used in colorectal cancer [Kurniali P et al 2010]. This clinical observation is supported by robust mechanobiological evidence [Ma Y et al. 2025]. Magnesium is not only a cofactor for DNA repair enzymes (Nucleotide Excision Repair) but is also critical for the cellular influx of platinum-based drugs (e.g., oxaliplatin) [Balint E, Unk I. 2023]. Patients with higher baseline Magnesium had significantly reduced odds of non-response. Mechanistically, Magnesium is an essential cofactor for enzymes involved in DNA repair (Nucleotide Excision Repair) and genomic stability [Fenech M. 2020]. While proficient DNA repair is sometimes associated with drug resistance, adequate magnesium is also required for the maintenance of cellular energy metabolism and the function of membrane transporters [Liu M, Dudley S 2025].

Recent studies indicate that platinum drugs enter cells via the high-affinity copper transporter CTR1, the stability and gating of which are modulated by magnesium [Harrach S, Ciarimboli G. 2015]. Hypomagnesemia, often exacerbated by the nephrotoxicity of the chemotherapy itself, may downregulate these transporters, effectively “locking the door” against the drug and leading to pharmacodynamic resistance [Workeneh B et al 2020]. Our results corroborate the findings of Wesselink et al., who demonstrated that magnesium intake is inversely associated with recurrence and mortality in colorectal cancer, suggesting that adequate magnesium status is permissive for optimal chemotherapeutic efficacy [Wesselink E et al. 2020]. Furthermore, observational studies have shown that patients who maintain normal magnesium levels during chemotherapy experience fewer dose-limiting toxicities (such as neurotoxicity), allowing for better adherence to the treatment schedule and consequently better outcomes [Sambataro D et al 2025]

Although serum Zinc levels were higher in the complete response group, this difference did not reach statistical significance. The higher levels found in responders align with Zinc’s role in stabi-

lizing the p53 tumor suppressor. Zinc is a vital component of the p53 tumor suppressor protein, which orchestrates apoptosis in response to chemotherapy-induced DNA damage [Al-Saran N et al 2016]. Functional p53 is required to trigger apoptosis following chemotherapy-induced DNA damage [Wu W et al 2021]. Zinc deficiency leads to p53 misfolding and a failure to execute cell death, promoting chemoresistance [Ha J et al 2022]. Wu and co-authors previously demonstrated that serum zinc levels are significantly lower in colorectal cancer patients compared to healthy controls and that deficiency correlates with advanced staging [Wu X et al 2020].

The elevated copper levels in non-responders mirror established literature linking hypercupremia to tumor angiogenesis and high tumor burden via the vascular endothelial growth factor pathway [Rigiracciolo D et al. 2015]. Copper chelation is currently being explored as a therapeutic strategy to starve tumors of their blood supply, supporting the notion that lower copper creates a more favorable landscape for treatment response [Tang X et al 2023]. Elevated serum copper is a well-documented phenomenon in various malignancies, including colorectal cancer, where it facilitates tumor angiogenesis via the activation of vascular endothelial growth factor and other proliferative pathways [Wang Y et al 2024]. Xing et al. reported that serum copper levels increase progressively with disease stage in colorectal carcinoma, serving as a marker of tumor burden [Xing Z et al 2025]. Our findings support the hypothesis that lower copper levels creates a less favorable microenvironment for tumor progression and metastasis, potentially enhancing the efficacy of cytotoxic agents [Kong R, Sun G. 2023]. The non-significant P-value suggests that while Copper may be a marker of disease extent, it may be less specific as a standalone predictor of immediate chemotherapy response compared to Magnesium in this specific patient subset.

**Limitations:** The interpretation of these results is constrained by the pilot nature of the study and the small sample size (n=30), which reduced the statistical power to detect subtler associations for Zinc and Copper. Additionally, the study was cross-sectional regarding biomarker measurement; longitudinal monitoring of trace elements during therapy would provide deeper insights into their dynamic relationship with treatment toxicity and

efficacy. Despite these limitations, the significant association found for Zinc provides a compelling basis for further investigation into nutritional stratification in gastric oncology.

### CONCLUSION

In conclusion, this study identifies baseline serum Magnesium as a potent and independent predictor of chemotherapy response in patients with colon cancer. The findings suggest that hypomag-

nesemia may be a modifiable risk factor for chemoresistance, potentially by impairing drug uptake mechanisms. While Zinc and Copper exhibited trends consistent with their roles in apoptosis and angiogenesis, Magnesium appears to be the most robust serum biomarker in this specific cohort. Routine screening and potential correction of magnesium levels prior to chemotherapy could represent a simple, cost-effective strategy to enhance therapeutic outcomes.

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### REFERENCES

1. Akhtar MJ, Ahamed M, Kumar S, Khan MM, Ahmad J, Alrokayan SA. (2012). Zinc oxide nanoparticles selectively induce apoptosis in human cancer cells through reactive oxygen species. *Int J Nanomedicine*. 2012;7:845-57. doi: 10.2147/IJN.S29129.
2. Arianmanesh F, Bagheri S, Karimi MA, Izadi S, Ahmadi MH. (2025). The Evaluation of Diagnostic, Prognostic, and Predictive Role of Hematologic Inflammatory Indices NLR, PLR, and LMR in Common Solid Tumors. *Cancer Rep (Hoboken)*. 2025 Dec;8(12):e70407. doi: 10.1002/cnr2.70407.
3. Al-Saran N, Subash-Babu P, Al-Nouri DM, Alfawaz HA, Alshatwi AA. (2016). Zinc enhances CDKN2A, pRb1 expression and regulates functional apoptosis via upregulation of p53 and p21 expression in human breast cancer MCF-7 cell. *Environ Toxicol Pharmacol*. 2016 Oct;47:19-27. doi: 10.1016/j.etap.2016.08.002.
4. Amhare AF, Liu H, Qiao L, Deng H, Han J. (2025). Elemental Influence: The Emerging Role of Zinc, Copper, and Selenium in Osteoarthritis. *Nutrients*. 2025 Jun 21;17(13):2069. doi: 10.3390/nu17132069.
5. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. (2017). Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66(4):683-691. doi: 10.1136/gutjnl-2015-310912.
6. Azizi Kia H, Teymourzadeh A, Kouchaki H, Nakhostin-Ansari A, Jafari Doudaran P, Ahmadijad I, et al. (2025). Colorectal Cancer Incidence in Iran Based on Sex, Age, and Geographical Regions: A Study of 2014-2017 and Projected Rates to 2025. *Arch Iran Med*. 2024 Apr 1;27(4):174-182. doi: 10.34172/aim.2024.26.
7. Balint E, Unk I. (2023). For the Better or for the Worse? The Effect of Manganese on the Activity of Eukaryotic DNA Polymerases. *Int J Mol Sci*. 2023 Dec 27;25(1):363. doi: 10.3390/ijms25010363.
8. Biller LH, Schrag D. (2021). Diagnosis and Treatment of Metastatic Colorectal Cancer: A Review. *JAMA*. 2021;325(7):669-685. doi:10.1001/jama.2021.0106.
9. Fenech M. (2020). The role of nutrition in DNA replication, DNA damage prevention and DNA repair. In *Principles of Nutrigenetics and Nutrigenomics 2020* Jan 1 (pp. 27-32). Academic Press. DOI:10.1016/B978-0-12-804572-5.00004-5
10. Fong CW. (2016). Platinum based radiochemotherapies: Free radical mechanisms and radiotherapy sensitizers. *Free Radic Biol Med*. 2016 Oct;99:99-109. doi: 10.1016/j.freeradbiomed.2016.07.006.
11. Gewandter JS, McDermott MP, He H, Gao S, Cai X, Farrar JT, et al. (2019). Demonstrating Heterogeneity of Treatment Effects Among Patients: An Overlooked but Important Step Toward Precision Medicine. *Clin Pharmacol Ther*. 2019 Jul;106(1):204-210. doi: 10.1002/cpt.1372.

12. Ghasemi-Kebria F, Jafari-Delouie N, Semnani S, Fazel A, Etemadi A, Norouzi A, et al. (2004). Colorectal cancer incidence trends in Golestan, Iran: An age-period-cohort analysis 2004-2018. *Cancer Epidemiol.* 2023 Oct;86:102415. doi: 10.1016/j.canep.2023.102415.
13. Górska A, Markiewicz-Gospodarek A, Trubalski M, Żerebiec M, Poleszak J, Markiewicz R. (2024). Assessment of the Impact of Trace Essential Metals on Cancer Development. *Int J Mol Sci.* 2024 Jun 21;25(13):6842. doi: 10.3390/ijms25136842.
14. Ha JH, Praelo O, Carpizo DR, Loh SN. (2022). p53 and Zinc: A Malleable Relationship. *Front Mol Biosci.* 2022 Apr 13;9:895887. doi: 10.3389/fmolb.2022.895887.
15. Harrach S, Ciarimboli G. (2015). Role of transporters in the distribution of platinum-based drugs. *Front Pharmacol.* 2015 Apr 24;6:85. doi: 10.3389/fphar.2015.00085.
16. Hassan M, Tutar L, Sari-Ak D, Rasul A, Basheer E, Tutar Y. (2024). Non-genetic heterogeneity and immune subtyping in breast cancer: Implications for immunotherapy and targeted therapeutics. *Transl Oncol.* 2024 Sep;47:102055. doi: 10.1016/j.tranon.2024.102055.
17. Kamiya T. (2022). Copper in the tumor microenvironment and tumor metastasis. *J Clin Biochem Nutr.* 2022 Jul;71(1):22-28. doi: 10.3164/jcfn.22-9.
18. Kim SE, Paik HY, Yoon H, Lee JE, Kim N, Sung MK. (2015). Sex- and gender-specific disparities in colorectal cancer risk. *World J Gastroenterol.* 2015;21(17):5167-5175.
19. Kong R, Sun G. (2023). Targeting copper metabolism: a promising strategy for cancer treatment. *Front Pharmacol.* 2023 Jul 26;14:1203447. doi: 10.3389/fphar.2023.1203447.
20. Kurniali PC, Luo LG, Weitberg AB. (2010). Role of calcium/ magnesium infusion in oxaliplatin-based chemotherapy for colorectal cancer patients. *Oncology (Williston Park).* 2010 Mar;24(3):289-92. PMID: 20394142.
21. Lawrence R, Watters M, Davies CR, Pantel K, Lu YJ. (2023). Circulating tumour cells for early detection of clinically relevant cancer. *Nat Rev Clin Oncol.* 2023 Jul;20(7):487-500. doi: 10.1038/s41571-023-00781-y.
22. Lei ZN, Tian Q, Teng QX, Wurpel JND, Zeng L, Pan Y, Chen ZS. (2020). Understanding and targeting resistance mechanisms in cancer. *MedComm* (2020). 2023 May 22;4(3):e265. doi: 10.1002/mco2.265.
23. Leng G, Duan B, Liu J, Li S, Zhao W, Wang S, et al. (2024). The advancements and prospective developments in anti-tumor targeted therapy. *Neoplasia.* 2024 Oct;56:101024. doi: 10.1016/j.neo.2024.101024.
24. Liu M, Dudley SC Jr. (2025). Magnesium Homeostasis and Magnesium Transporters in Human Health. *Nutrients.* 2025 Mar 6;17(5):920. doi: 10.3390/nu17050920.
25. Ma Y, Wang Y, Song S, Yu X, Xu C, Wan L, et al. (2025). Mechanism and application prospect of magnesium-based materials in cancer treatment. *Journal of Magnesium and Alloys.* 2025 Mar 4. <https://doi.org/10.1016/j.jma.2025.02.010>
26. Majek O, Gondos A, Jansen L, Emrich K, Holleczer B, Katalinic A, et al. (2013). Sex differences in colorectal cancer survival: population-based analysis of 164,996 colorectal cancer patients in Germany. *PLoS One.* 2013 Jul 5;8(7):e68077. doi: 10.1371/journal.pone.0068077.
27. Passaro A, Al Bakir M, Hamilton EG, Diehn M, André F, Roy-Chowdhuri S, et al. (2024). Cancer biomarkers: Emerging trends and clinical implications for personalized treatment. *Cell.* 2024 Mar 28;187(7):1617-1635. doi: 10.1016/j.cell.2024.02.041.
28. Puca R, Nardinocchi L, Porru M, Simon AJ, Rechavi G, Leonetti C, et al. (2011). Restoring p53 active conformation by zinc increases the response of mutant p53 tumor cells to anticancer drugs. *Cell Cycle.* 2011 May 15;10(10):1679-89. doi: 10.4161/cc.10.10.15642.
29. Rafieemehr H, Farmany A, Ghorbani S, Jafari M, Behzad MM. (2024). Serum Trace Element Levels in Cancer Patients Undergoing Chemotherapy: a Before-After Analysis. *Biol Trace Elem Res.* 2024 Oct;202(10):4367-4374. doi: 10.1007/s12011-023-04025-z.
30. Rahimi F, Rezaatmand R, Tabesh E, Tohidinik HR, Hemami MR, Ravankhah Z, Adibi P. (2024). Incidence of colorectal cancer in Iran: A systematic review and meta-analysis. *J Res*

- Med Sci. 2024 Oct 24;29:65. doi: 10.4103/jrms.jrms\_110\_23.
31. Rigracciolo DC, Scarpelli A, Lappano R, Pisano A, Santolla MF, De Marco P, et al. (2015). Copper activates HIF-1 $\alpha$ /GPER/VEGF signalling in cancer cells. *Oncotarget*. 2015 Oct 27;6(33):34158-77. doi: 10.18632/oncotarget.5779.
32. Sambataro D, Scandurra G, Scarpello L, Gebbia V, Dominguez LJ, Valerio MR. (2025). A Practical Narrative Review on the Role of Magnesium in Cancer Therapy. *Nutrients*. 2025 Jul 9;17(14):2272. doi: 10.3390/nu17142272.
33. Siegel RL, Giaquinto AN, Jemal A. (2024). Cancer statistics, 2024. *CA Cancer J Clin*. 2024 Jan-Feb;74(1):12-49. doi: 10.3322/caac.21820. Epub 2024 Jan 17. Erratum in: *CA Cancer J Clin*. 2024 Mar-Apr;74(2):203. doi: 10.3322/caac.21830.
34. Singh A. (2024). Global burden of five major types of gastrointestinal cancer. *Prz Gastroenterol*. 2024;19(3):236-254. doi: 10.5114/pg.2024.141834.
35. Tang X, Yan Z, Miao Y, Ha W, Li Z, Yang L, Mi D. (2023). Copper in cancer: from limiting nutrient to therapeutic target. *Front Oncol*. 2023 Jun 23;13:1209156. doi: 10.3389/fonc.2023.1209156.
36. Ullah MI, Manni E, Shakil M, Hussain S, Awan AN, Hussain S, et al. (2025). Association of serum copper, zinc and copper to zinc ratio in patients with acute myeloid leukemia. *Scientific Reports*. 2025 Sep 30;15(1):1-9. <https://doi.org/10.1016/j.exger.2025.112963>
37. Wang Y, Pei P, Yang K, Guo L, Li Y. (2024). Copper in colorectal cancer: From copper-related mechanisms to clinical cancer therapies. *Clin Transl Med*. 2024 Jun;14(6):e1724. doi: 10.1002/ctm2.1724.
38. Wesselink E, Kok DE, Bours MJL, de Wilt JHW, van Baar H, van Zutphen M, et al. (2020). Vitamin D, magnesium, calcium, and their interaction in relation to colorectal cancer recurrence and all-cause mortality. *Am J Clin Nutr*. 2020 May 1;111(5):1007-1017. doi: 10.1093/ajcn/nqaa049.
39. White A, Ironmonger L, Steele RJC, Ormiston-Smith N, Crawford C, Seims A. (2018). A review of sex-related differences in colorectal cancer incidence, screening uptake, routes to diagnosis, cancer stage and survival in the UK. *BMC Cancer*. 2018 Sep 20;18(1):906. doi: 10.1186/s12885-018-4786-7.
40. Wong CP, Beaver LM, Ho E. (2025). Protective role of dietary zinc on DNA damage, oxidative stress, and metal toxicity. *Front Mol Biosci*. 2025 Jun 24;12:1618318. doi: 10.3389/fmolb.2025.1618318.
41. Workeneh BT, Uppal NN, Jhaveri KD, Rondon-Berrios H. (2020). Hypomagnesemia in the Cancer Patient. *Kidney360*. 2020 Nov 11;2(1):154-166. doi: 10.34067/KID.0005622020.
42. Wu W, Wei T, Li Z, Zhu J. (2021). p53-dependent apoptosis is essential for the antitumor effect of paclitaxel response to DNA damage in papillary thyroid carcinoma. *Int J Med Sci*. 2021 Jul 11;18(14):3197-3205. doi: 10.7150/ijms.61944.
43. Wu X, Wu H, Liu L, Qiang G, Zhu J. (2020). Serum zinc level and tissue ZIP4 expression are related to the prognosis of patients with stages I-III colon cancer. *Transl Cancer Res*. 2020 Sep;9(9):5585-5594. doi: 10.21037/tcr-20-2571.
44. Xing Z, Xiao Y, Li S, Jia G, Cheng P, Chen Y, et al. (2025). Analysis and exploration of the association between serum tumor marker status and clinical pathological features, as well as efficacy, in colorectal cancer. *Oncol Lett*. 2025 Jul 9;30(3):438. doi: 10.3892/ol.2025.15184.
45. Zhou S, Song X, Zeng W, Chen D. (2024). Targeting Ion Channels for Cancer Therapy: From Pathophysiological Mechanisms to Clinical Translation. *Pharmaceuticals (Basel)*. 2025 Oct 10;18(10):1521. doi: 10.3390/ph18101521.



## CONTENTS

4. **DAS A.C., SAMIR P.V., KHAN S.H., FERNANDES B., ARYA A., MUSTAFA M.**  
ARTIFICIAL INTELLIGENCE IN THERAPEUTIC DECISION-MAKING FOR COMPLEX DENTAL DISEASES: A REVIEW
11. **ALAM M.K. ALMOHAMMED Y.E.M., HAJEER M.Y., ALANAZI A.W.N., ALANAZI F.S.A., ALNAWMASI Y.M.F.**  
LABORATORY ASSESSMENT OF CRISPR-MEDIATED MODULATION OF OSTEOBLASTIC AND OSTEOCLASTIC GENE EXPRESSION UNDER SIMULATED ORTHODONTIC FORCE
17. **GEORGE A.L., PANICKER P., FRANCIS F., RAGHUNANDANAN S., MOHIDEEN K., ALMUTAIRY M.F.**  
CAR-T-INSPIRED IMMUNOMODULATORY NANOVESICLES FOR TARGETED ELIMINATION OF ORAL SQUAMOUS CELL CARCINOMA CELLS
23. **ALFAWZAN A.A., ALAM M.K., HAJEER M.Y.**  
IN-VITRO EVALUATION OF NANOPARTICLE-REINFORCED ORTHODONTIC ADHESIVES FOR ENHANCED SHEAR BOND STRENGTH AND ANTIMICROBIAL ACTIVITY
30. **JADHAV S., PATRI G., BEHERA S.S.P., BANIK A., ARYA A., MUSTAFA M.**  
STEM-CELL-DERIVED BIOENGINEERED DENTAL PULP CONSTRUCTS FOR VITAL PULP THERAPY: A RANDOMIZED LABORATORY TRIAL
36. **TUENKAR Y.A., SHANKARGOUDA S., SEHDEV B., SINGH R.B., RAMAMURTHY J., MAHAPATRA N.**  
AI-GUIDED PERSONALIZED DRUG-DELIVERY NANOPARTICLES FOR PRECISION TREATMENT OF PERI-IMPLANTITIS: A MULTICENTER EVALUATION
42. **SADAT MANSOURI S., DADEHBEIGLOU P., NEMATI ANARAKI S., RAHMATPANAH K.**  
CYANOACRYLATE VS. DENTIN BONDING ON REDUCING DENTAL SENSITIVITY
50. **JALALUDDIN M., CALIAPEROMAL S.K., JAYANTI I., PATIL M., RAMAMURTHY J., MUSTAFA M.**  
MRNA-BASED REGENERATION OF PERIODONTAL LIGAMENT FIBROBLASTS: A TRANSLATIONAL PILOT STUDY
56. **AZATYAN V.YU., YESSAYAN L.K., SHMAVONYAN M.V., MURADYAN A.A.**  
EVALUATING THE EFFECTS OF CIGARETTE SMOKING AND HEATED TOBACCO PRODUCTS ON THE ORAL MUCOSA AND PERIODONTIUM IN PATIENTS WITH HEPATIT C VIRUS IN ARMENIA: A PILOT STUDY
65. **MOHAMMADI E., NAZARBAGHI S., HAJIESMAELLO M.**  
COMPARATIVE EFFICACY OF LOW-LEVEL LASER THERAPY AND TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION IN THE MANAGEMENT OF DIABETIC PERIPHERAL NEUROPATHY: A RANDOMIZED CONTROLLED TRIAL
73. **HOSSEINIAZAR M.M., KABOUDMEHRI M., ROOSTA Y.**  
PREDICTIVE VALUE OF SERUM TRACE ELEMENTS FOR CHEMOTHERAPEUTIC EFFICACY IN GASTRIC AND COLON CANCER: A CROSS-SECTIONAL STUDY
82. **ESMAELIZADEH M., ASHT'A'RI MEHRJARDI A., MOHAMMADINIA O., MOHAMMADPOUR S., HOKMABADI M.E., AMINI F., AZIZI T., VAKILI AHRARI RODI M.**  
NEW HORIZONS IN SUBSTANCE ABUSE DISORDER: A SYSTEMATIC REVIEW OF EPIGENETIC MECHANISMS AND MULTIDIMENSIONAL PERSPECTIVES (2023–2025)
90. **SHAHROKHI-FARD P., SAGHEBI A., TALAEI A.**  
EFFECTIVENESS OF ACCEPTANCE AND COMMITMENT THERAPY ON COVID-19 PROTECTION INDICATORS, PHYSICAL DISORDER SYMPTOMS, AND PERCEIVED STRESS IN HEALTHCARE PERSONNEL IN MASHHAD HOSPITALS
98. **SURKUNDA T.S., STANLEY W., ELENJICKAL V., BALLAL A., NAGARAJU S., BOPPE S., KAMATH N., SHASTRY B.**  
CLINICAL FEATURES, OUTCOMES AND COMPARATIVE EVALUATION OF DIAGNOSTIC CRITERIA OF INVASIVE ASPERGILLOSIS AT A TERTIARY CARE CENTRE: A RETROSPECTIVE OBSERVATIONAL STUDY
- 108 **SABERI M.K., MOKHTARI H., HOSEINI AHANGARI S.A., OUCHI A., SHOURCHEH B.**  
THE ONLINE ATTENTION TO SPIRITUAL HEALTH RESEARCH: AN ALTMETRIC ANALYSIS
- 118 **LETTER TO THE EDITOR**  
A GENERALIZED ANALYTICAL REVIEW OF ARTICLES IN A ISSUE 2 ON ADVANCED TECHNOLOGIES IN MODERN STOMATOLOGY



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