

Zinc in Cancer Therapy Revisited

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ABSTRACT Zinc is a trace element, which is abundant in nature. It is also an essential and important micronutrient found in many foods. It has a role in multiple bodily processes including wound healing and boosting of the immune system. This review shows evidence of zinc deficiency in cancer patients of all types, a deficiency that correlates with disease severity and negatively correlates with survival rates. Lower zinc levels led to more severe and advanced disease symptoms and to lower survival rates. This review shows studies of Zinc, as a nanoparticle and as a photosensitizer in photodynamic therapy in various combinations with other substances. This review also shows the cytotoxicity and tumor suppressive ability of zinc in studies conducted both in vitro and in vivo. This result has been shown in all types of cancer tested. Zinc has exhibited toxicity toward cancer cells without showing any side effects toward healthy cells. It is, therefore, recommended that zinc be added to cancer treatment regimens to alleviate zinc deficiency in cancer patients and perhaps to treat cancer as a whole.

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Zinc is the 24th most abundant element in Earth's crust. It plays an important role in nutrition and in human health. The recommended daily intake is between 9–11 mg per day was lately updated.

Animal products such as meat, fish, shellfish, fowl, eggs, and dairy contain zinc. The concentration of zinc in plants varies with the level in the soil. With adequate zinc in the soil, the food plants that contain the most zinc are wheat (germ and bran) and various seeds, including sesame, poppy, alfalfa, celery, and mustard. Zinc is also found in beans, nuts, almonds, whole grains, pumpkin seeds, sunflower seeds, and blackcurrant.

Zinc has a role in many cellular processes; some of which have not yet fully been established in research. Importantly, it is vital to proper immune system function and in wound healing. Ibs and Rink reported that when peripheral blood mononuclear cells

are incubated with zinc in vitro, the release of cytokines such as interleukins (IL)-1 and IL-6, tumor necrosis factor- α , soluble IL-2R, and interferon- γ is induced [1].

Zinc deficiency among cancer patients have been compared to levels found in controls [2-7]. This insufficiency negative-

ly correlates with survival rates and disease progression. Zinc nanoparticles [8-26] and zinc in different constellations [27-40] have been shown to be efficient anti-cancer agents and tumor suppressors, both in vitro and in vivo, while having no toxic effect on normal cells. Therefore, inclusion of zinc supplementation may become part of the treatment protocol for cancer patients.

METHODS

From 2018 until 2021, I regularly searched the term *zinc cancer* in the Google search engine. I used various search options and gathered all relevant articles and information.

ZINC LEVELS IN BLOOD AND TISSUE OF CANCER PATIENTS

Studies showing zinc deficiency among cancer patients tend to correlate with disease progression and lower survival. The research also has shown cancerous tissue to be devoid of zinc compared to healthy tissue.

Hashemi et al. [2] evaluated zinc and selenium levels among breast cancer patients compared with controls. They found that mean zinc levels were 689.57 ± 146.13 mg/dl in the patient group and 874.85 ± 150.53 mg/dl in the control group [2].

Issell and colleagues [3] studied serum zinc levels in lung cancer patients. They found subnormal zinc levels in 24 of 26 patients and reported a significant ($P=0.007$) survival advantage for those patients with pretreatment zinc concentrations > 45 μ g.

Isriss and co-authors [4], in a study conducted in Khartoum, found zinc and iron deficiency among Sudanese women with breast cancer. They reported that the serum level of zinc and iron were significantly lower in women with breast cancer and significant with different stage of disease. At stage 1, zinc levels were 0.918 ± 0.25 vs. 0.443 ± 0.05 at stage 2 and 0.259 ± 0.06 at stage 3.

Christudoss et al. [5] examined healthy and cancerous tissue from the stomach and colon and found cancerous tissue to be devoid of zinc. They found a decrease of 68% and 66% compared to healthy tissue in stomach and colon cancerous tissue, respectively [5].

Another study, by Mocchegiani and colleagues [6] checked the plasma zinc levels in leukemia patients through different stages of the disease: The average zinc level at diagnosis was 59.3 μ /dl while at complete remission it was 90.8 μ /dl. The plasma zinc levels during relapse were approximately 72.8 μ /dl

ZINC DEFICIENCY AMONG CANCER PATIENTS CORRELATES WITH DISEASE SEVERITY AND POORER SURVIVAL RATES

while off-therapy they were 107.5 µ/dl. In age-matched healthy controls the average zinc level was 112 µ/dl [6].

Lubiński et al. [7] checked for zinc levels and their correlation with survival. They found that in laryngeal cancer patients in the lowest tertile of zinc levels, 50 of 99 patients died in the 5-year follow-up period, in the medium tertile 37 of 99 died, and in the highest tertile for zinc levels among cancer patients only 29 of 102 died. [7]. [Table 1].

Table 1. Zinc levels in cancer patients in Poland and their correlation to survival rates

Zinc level, µg	Dead (%)	Living (%)	Survival rate
357.76-578.71	50	49	49.5%
579.17-687.98	37	62	62.6%
688.54-1317.87	29	73	71.5%

ZINC NANOPARTICLES, IN VITRO

Plenty of research has been conducted regarding zinc nanoparticles synthesized by different methods. This form of zinc intervention has gained momentum, and approximately half of the studies in zinc treatment related to cancer are centered on these particles.

Wu and Zhang [8] observed that the zinc oxide nanoparticle and chitosan-assembled zinc oxide nanoparticles showed significant cytotoxicity in cervical cancer cells in a concentration-dependent manner.

Wang et al. [9] found that zinc oxide nanoparticles were able to target multiple cell types of cancer, including cancer cells, cancer stem cells, and macrophages. They simultaneously performed several key functions, including inhibition of cancer proliferation, sensitization of drug-resistant cancer, prevention of cancer recurrence and metastasis, and resuscitation of cancer immunosurveillance.

Ahmad et al. [10] found that the bio-nanocomposite of polypyrrole and chitosan formulation (Ppy/C/Z) showed excellent anti-bacterial and anti-cancer activity compared to a pristine (Ppy/C). The apoptosis data with varying concentrations of Ppy/C/Z reveal the remarkable activity against these cancer cell lines.

Ruantong and co-authors [11] noted that the synthesized zinc oxide nanosheets demonstrated potent anti-cancer activity against cell viability of skin cancer cell (A431), colorectal cancer cell (SW620), and liver cancer cell (HepG2) without affecting normal cell line.

Vafei and colleagues [12] reported that the percentage of early and late apoptotic cells was 78.2% in those treated with Zn-PNPs. Whereas D'Souza et al. [13] reported that ZnOVI nanostructures exhibited up to 91.18 ± 1.98% human triple negative breast cancer suppressive activity.

Last, Boroumand Moghaddam et al. [14] reported that zinc oxide nanoparticles were cytotoxic to the MCF-7 cells in a dose-dependent manner. The 50% growth inhibition concentration (IC50) of zinc oxide nanoparticles at 24 hours was 121 µg/ml. Cell cycle analysis revealed that zinc oxide nanoparticles in-

duced sub-G1 phase (apoptosis), with values of 1.87% at 0 µg/ml (control), 71.49% at IC25, 98.91% at IC50, and 99.44% at IC75.

Zinc nanoparticles show incredible tumor suppressive results and anti-cancer activity in a dose-dependent manner and that they are selectively toxic only to cancer cells without harming regular cells.

ZINC NANOPARTICLES, IN VIVO

There are few in vivo studies on zinc nanoparticles. Most were conducted on mouse and rat models [15-20]. Most of the results concur with the in-vitro studies:

Xu et al. [15] reported that Zn-CuONPs could inhibit tumor growth both in vitro and in vivo significantly.

Tanino and colleagues [16] found out that ZnO nanoparticles were genotoxic against small-cell lung cancer cells and resulted in low viability, even in cells orthotopically grafted onto mouse models. However, the nanoparticles were less cytotoxic against normal lung-derived cells and did not elicit observable adverse effects after intravenous administration.

Morsy and co-authors [17] found that the survival time of mice was improved in all ZnO NP-treated groups, especially in EACs-bearing mice treated with ZnO NPs at a dose of 10 mg/kg every other day.

Bobrowska-Korczak et al. [18] noted that biopsy images indicated grade 1 tumors with multiple inflammatory infiltrates in the group treated with zinc nanoparticles, whereas, in the other groups, a moderately differentiated grade 2 adenocarcinoma was identified.

Yang et al. [19] showed that they say "displays the outcome of BAP (a carcinogen) induction and ZnO-SYR on lung and body weight, and tumor occurrence [Table 2]. Results showed decreased body weight (*P* < 0.05), augmented lung weight, and increased tumor induction in BAP-only treated group-II mice compared to controls (group 1: A,G). While post-initiation with ZnO-SYR (20 mg/kg body weight) and BAP demonstrated the improved body weight and decreased lung weight in cancer-bearing animals (group III). While in ZnO-SYR (20 mg/kg body weight) only treatment in group IV animals markedly improved the bodyweight and abrogated the tumor occurrence [19].

Table 2. Outcome of BAP introduction and ZnO-SYR on lung weight, body weight, and tumor occurrence in mice, [19]

Parameters	Body weight, grams	Lung weight, mg	Tumor incidence
Group 1	30.76 ± 6.62	232 ± 52.93	0
Group 2	20.73 ± 3.21*	317 ± 62.77*	6
Group 3	26.23 ± 4.87**	265 ± 7.14**	3
Group 4	32.14 ± 7.99**	244 ± 54.62**	0

Values are expressed as mean ± standard deviation (n=3)

**P* < 0.05, group 2 compared to group 1 (control)

***P* < 0.01, group 3 and group 4 compared to group 2

There were 6 mice in each group tested. Group 1 acted as the control group [19].

Bashandy et al. [20] concluded that the treatment of hepatocellular carcinoma rats with ZnO-NPs offered an anticancer remedy that may be considered as a new trend for control HCC.

The in vivo results match the results seen in vitro, even if in a smaller sample size. Once again, Zinc's outstanding anti-cancer properties are observed.

ZINC AS A PHOTOSENSITIZER IN PHOTODYNAMIC THERAPY

An emerging target of research is photodynamic therapy (PDT). This therapy uses light (or laser) irradiation to treat cancer cells [21]. Zinc has been tested as a photosensitizer in this technique and has shown exceptional results [22-26].

Gao et al. [22] report that HA-es-ZnPP showed lower but comparable intracellular uptake and cytotoxicity in cultured mouse C26 colon cancer cells compared to native ZnPP. More importantly, light irradiation resulted in a 10-time increased cytotoxicity, which is the PDT effect. In a mouse sarcoma S180 solid tumor model, HA-es-ZnPP as polymeric micelles exhibited a prolonged systemic circulation time and the consequent tumor-selective accumulation based on the enhanced permeability and retention (EPR) effect was evidenced. Consequently, a remarkable anticancer PDT effect was achieved using HA-es-ZnPP and a xenon light source, without apparent side effects [22].

While Gao and Lo [23] reported that the DOX-ZnPc-micelles could induce cell death mainly through apoptosis and exhibit preferential tumor retention in tumor-bearing mice.

Dai et al. [24] found that with the help of *Escherichia coli* (E. coli), E. coli@ZnPc-IR710 presented a significantly enhanced cytotoxicity on human breast cancer MCF-7 cells compared with ZnPc-IR710 (survival rate of tumor cells was 39% vs. 57% at a concentration of 50 nmol L⁻¹). Moreover, in vivo study showed that E. coli@ZnPc-IR710 inhibited the tumor growth and resulted in a complete tumor growth suppress in subcutaneous mouse 4T1 breast tumor model.

Nackiewicz and colleagues [25] showed that photoactivated ZnPcOC (30 μM) was able to reduce the cell viability of melanoma and fibroblast to about 50%, respectively.

Ogobodu et al. [26] reported that ZnPc-PDT treatment of HCC cells in vivo using CAM assay resulted in > 80% decrease in tumor size with a viable embryo in hepatocellular carcinoma.

Zinc possesses enormous cytotoxicity, which is evident in different kinds of interventions.

ZINC IN COMBINATION WITH OTHER SUBSTANCES

Zinc in combination with other substances has been shown to have cytotoxic properties. In these essays, we're reported once again of exceptional anti cancerous effect by zinc, when coupled with all sorts of drugs and treatments. In many cases, the

naked zinc has better properties than the aligned substance, but in some reports the combination boosts even the effect of zinc.

By using Hoechst staining and flow cytometry, Zhang et al. [27] found that zinc enhanced PC-3-cell chemosensitivity to paclitaxel.

Toren et al. [28] reported that in vitro cell viability analysis showed that the cytotoxic activity of TMZ was substantially increased with addition of zinc. The co-treatment resulted in significant reduction in tumor volume in TMZ/zinc treated mice relative to treatment with TMZ alone. However, Margalit and colleagues [29] noted that these tumors were resistant to adriamycin treatment and that zinc suppresses tumor growth in vivo in these mice.

Brar et al. [30] studied zinc in combination with disulfiram. They found that disulfiram inhibited growth and angiogenesis in melanomas transplanted in severe combined immunodeficient mice, and these effects were potentiated by Zn²⁺ supplementation. The combination of oral zinc gluconate and disulfiram at currently approved doses for alcoholism also induced > 50% reduction in hepatic metastases and produced clinical remission in a patient with stage IV metastatic ocular melanoma.

Hu and Du [31] studied zinc nanoparticles in combination with cisplatin and gemcitabine. Their results suggested that NS-CLC therapy with ZnO-NPs(Cp/Gem) could enhance the cytotoxic action of chemotherapeutic agents synergistically, indicating a promising potential for ZnO-NPs in antitumor applications.

Xin et al. [32] studied the combination of zinc and aspartic acid. They found that the zinc-aspartic acid nanofibers had specific binding ability to eHSP90, which induced a decrease in the level of the tumor marker-gelatinases, consequently resulting in downregulation of the tumor-promoting inflammation nuclear factor-kappa B signaling, and finally inhibiting cancer cell proliferation, migration, and invasion; while they are harmless to normal cells [32].

Nabil and co-authors [33] studied zinc in combination with sorafenib. They reported that ZnO-NPs synergized with sorafenib as a combination therapy to execute more effective and safer anticancer activity compared to monotherapy as shown by a significant reduction in tumor weight, tumor cell viability, and cancer tissue glutathione amount as well as by significant increase in tumor growth inhibition rate, DNA fragmentation, reactive oxygen species generation.

Pairoj et al. [34] reported that the carboplatin (CP)-doxorubicin (DOX)-ZnO complex under UV light irradiation exhibited high sensitivity toward human breast adenocarcinoma cells without affecting human keratinocyte immortal cells with an IC50 of 0.137 μg/ml, whereas the loading capacity and efficiency of CP-DOX-ZnO were 77.81% and 99.05%, respectively.

These studies showed that zinc, together with other substances, has a cytotoxic effect in all kinds of settings and combinations. It further reinforces what we learned about zinc's potency as a tumor suppressor and anti-cancer agent.

ZINC IN MANY DIFFERENT CONSTELLATIONS SHOWS ENORMOUS PROMISE AS A TUMOR SUPPRESSOR

ZINC TREATMENT IN DIFFERENT CONSTELLATIONS

Several studies did not meet the criteria for inclusion with regard to zinc interventions; however, they are on par with the previous studies on zinc nanoparticles, zinc in photodynamic therapy, and zinc in combinational therapies [35-38].

Hirai et al. [35] observed that LL/2-tumors were found in 88% (7/8) vehicle-treated mice, whereas tumors were found in 38% (3/8) and 25% (2/8) mice treated with 5 and 20 microg/mouse ZnPPIX (zinc protoporphyrin IX), respectively ($P = 0.0302$). Tumor growth was inhibited dose-dependently by ZnPPIX.

Srivastava et al. [36] found out that in depth characterization resulted in identification of pyrithione zinc (PYZ) as the most effective cytotoxic agent inhibiting cell proliferation and inducing apoptosis in OSCC cells in vitro. Furthermore, treatment with PYZ reduced colony forming, migration, and invasion potential of oral cancer cells in a dose-dependent manner. Importantly, PYZ treatment significantly reduced tumor xenograft volume in immunocompromised NOD/SCID/Crl mice without causing apparent toxicity to normal tissues." [36]

Kim et al. [37] reported on an intervention to human papillomavirus infection with zinc and citrate. The treatment included 12 weeks of a zinc citrate solution and resulted in the elimination of HR-HPV in 49 of 76 patients (64.47%) compared to the spontaneous clearance of 18 of 118 (15.25%) in the control group.

Ali et al. [38] reported that the zinc metal ion complex was the most active with 83.60 and 88.52% inhibitions for A549 and H1299 lung cancer lines at 20 mM concentration.

In various settings, zinc's properties are still observed. It seems that zinc in all forms is cytotoxic, which means intervention does not have to be delivered through nanoparticles or photodynamic therapy, even though most studies revolved around these methods. Perhaps the simplest easiest way of zinc supplementation could prove the most effective.

CASE STUDY

Eby [39] investigated the treatment of a girl with acute lymphocytic leukemia. He found low blood levels of zinc were often noted in acute lymphocytic leukemia (ALL), but zinc was not administered as part of any modern chemotherapy program in the treatment of ALL. He noted low blood levels of zinc in a 3-year-old girl who weighed 11.3 kg. Zinc was administered at the rate of 3.18 mg/kg body weight/day from the start of chemotherapy through the full 3 years of maintenance therapy. Dosage was split with 18 mg given at breakfast and 18 mg zinc with supper. The result was a bone marrow remission from 95+% blast cells to an observed zero blast cell count in both hips within the first 14 days of treatment which never relapsed.

Eby also found that in addition to the reduction of blast cells to an observed count of zero (not a single leukemic or normal blast), red blood cell production and other hemopoietic functions returned to normal at a clinically remarkable rate. There were no

side effects from zinc or chemotherapy at any time, and zinc was thought to have improved the patient's overall ability to withstand toxic effects of chemotherapy. The findings identified zinc treatment as being vital to rapid and permanent recovery from ALL.

A CASE-CONTROL, RANDOMIZED STUDY

The only research I could find regarding zinc supplementation to human cancer patients under cases-controls setting was conducted by Federico and colleagues [40]. They reported on a case of gut cancer. The study parameters focused on the nutritional status of patients and they did not look at zinc's tumor-suppressive features or at cancer cell viability pre- and post-treatment, at all. They studied body mass, fat mass, protein levels, and other mostly nutritional parameters. The dosage of zinc supplementation was low, only 21 mg per day. Eby [39], in his case report, gave almost twice as much to a 3-year-old girl.

Federico's group studied zinc supplementation in addition to selenium, another essential micronutrient that has been found to be deficient in cancer patients. They added supplements for 60 days in addition to the chemotherapy. Both in the basal condition and at 60 days, all patients were malnourished. Selenium and zinc concentrations were significantly lower ($P < 0.01$), whereas copper concentration was significantly higher ($P < 0.01$) in cancer patients than in control subjects. However, 21/30 patients (70%) treated with selenium and zinc did not show a further worsening of nutritional status and experienced a significant decrease of asthenia with an increase of appetite. However, 24/30 untreated patients (80%) had a significant decline of all parameters studied after 60 days [40].

CONCLUSIONS

Zinc deficiency among cancer patients correlates with disease progression and negatively correlates with survival rates. Zincs showed exceptional cytotoxicity both in in vitro and in in vivo despite small sample sizes. Promising results were confirmed in two studies conducted on humans.

Based on the accumulated data shown in this review, one may conclude that zinc supplementation not only fixes the zinc deficiency found in cancer patients, but also treats cancer as a whole. It is therefore recommended that zinc become a part of cancer treatment protocol, sooner rather than later.

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Don't get so tolerant that you tolerate intolerance.

Bill Maher (born 1956), comedian, actor, and writer

Hofstadter's Law: It always takes longer than you expect, even when you take into account Hofstadter's Law.

Douglas Hofstadter (born 1945), American professor of cognitive science, physics, and comparative literature