Opposing effects of low versus high concentrations of vitamins/dietary ingredients Vitamin C and niacin on colon cancer stem cells (CSCs)

Study Abstract

Colorectal cancer is one of the global causes of cancer deaths. Cancer stem cells (CSCs) inside the tumour niche responsible for metastasis and relapses, and hence need to be targeted for cancer therapeutics. Although dietary fibre and lifestyle changes have been recommended as measures for colorectal cancer prevention, no such recommendations are available for using water soluble vitamins as prophylaxis measure for colorectal cancers. **High dose of Vitamin C has been proven to selectively kill colon cancer cells having BRAF and KRAS mutations by inducing oxidative stress. In this study, we show for the first time the opposing effects of the low and high dose of Vitamin C and vitamin B3 on colon CSCs isolated from HT-29 and HCT-15 colorectal carcinoma cell lines. At small doses, both of these vitamins exerted a cell proliferative effect only on CSCs, while there was no change in the proliferation status of non-stem cancer cells and wild-type (WT) populations.** On the other hand, the death effects induced by high doses of Vitamin C and B3 were of the order of 50–60% and ~30% on CSCs from HT-29 and HCT15, respectively. Interestingly, the control fibroblast cell line (NIH3T3) was highly refractory all the tested concentrations of Vitamin C and B3, except for the highest dose – 10,000 µg of Vitamin C that induced only 15% of cell death. Hence, these results indicate the future scope of use of therapeutic doses of Vitamin C and B3 especially in patients with advanced colorectal cancer.

Opposing effects of low versus high concentrations of water soluble vitamins/dietary ingredients Vitamin C and niacin on colon cancer stem cells (CSCs), *Utsav Sen, Sudheer Shenoy P, Bipasha Bose, Cell Biol Int. 2017 Oct;41(10):1127-1145. doi: 10.1002/cbin.10830. Epub 2017 Aug 24.*

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24W500 Maple Ave Suite 107 Naperville IL 60540
OwenFonorow@inteligentVitaminC.com

Cell types and percentage of cell proliferation

Vitamin C conc. µM	HT-29 WT	HCT-15 WT	HT-29-CD44+	HCT-15 CD44+	HT-29-CD44−	HCT-15 CD44−
0	100	100	100	100	100	100
5	114	108	172	107	86	122
10	104.7	114	160.8	107.26	93.11	121.01
15	95.81	121.03	172	110.15	97.1	106
20	90.57	94.19	169.73	115.01	99.2	93.79
25	88.48	90.01	169.73	116.32	86.59	98.13
100	21.51	89.01	68.28	93.79	14.23	96.15
200	21.81	88.06	69.34	73.58	14.13	96.52
500	23.56	85.42	67.23	72.01	12.68	95.16
1,000	24.34	83.12	65.81	69.56	11.59	88.06
10,000	27.06	226	61.18	304.10	14.13	233.03

Table 2. Percentage of cell proliferation upon exposure to low (5–25 µM) and high concentration ranges (100–10,000 µM) of **vitamin C/ascorbic acid** in various cell populations obtained from HT-29 and HCT-15 colorectal carcinoma cell lines respectively. Table showing the respective percentages of cell proliferation of the cell populations WT, CSCs (CD44+) and non-stem cancer cells (CD44−) with respect to various concentrations (5–10,000 µM) of Vitamin C/Vitamin C from HT-29 and HCT-15 cell lines. The untreated control cells for each of the cell type WT, CSCs (CD44+) and non-stem cancer cells (CD44−) have been assigned an arbitrary value of 100% cell proliferation

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OwenFonorow@inteligentVitaminC.com

Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice

Daniel Couturier wrote: "I cannot comprehend why even proponents of high dose vitamin C consider it to be an inferior resource when it comes to antagonizing malignancies, considering the fact that available studies indicate that at doses of 4 g / kg b.w. a pancreatic tumor mass reduction of more than 40% could be achieved in a xenograft animal model. "

Study Abstract

Ascorbic acid is an essential nutrient commonly regarded as an antioxidant. In this study, we showed that ascorbate at pharmacologic concentrations was a prooxidant, generating hydrogen-peroxide-dependent cytotoxicity toward a variety of cancer cells in vitro without adversely affecting normal cells. To test this action in vivo, normal oral tight control was bypassed by parenteral ascorbate administration. Real-time microdialysis sampling in mice bearing glioblastoma xenografts showed that a single pharmacologic dose of ascorbate produced sustained ascorbate radical and hydrogen peroxide formation selectively within interstitial fluids of tumors but not in blood. Moreover, a regimen of daily pharmacologic ascorbate treatment significantly decreased growth rates of ovarian ($P < 0.005$), pancreatic ($P < 0.05$), and glioblastoma ($P < 0.001$) tumors established in mice. Similar pharmacologic concentrations were readily achieved in humans given ascorbate intravenously. These data suggest that ascorbate as a prodrug may have benefits in cancers with poor prognosis and limited therapeutic options.

Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice, *Proc Natl Acad Sci U S A. 2008 Aug 12; 105(32): 11105–11109. Published online 2008 Aug 4. doi: 10.1073/pnas.0804226105*
PMCID: PMC2516281 Qi Chen,† Michael Graham Espey,*†‡ Andrew Y. Sun,* Chaya Pooput,§ Kenneth L. Kirk,§ Murali C. Krishna,¶ Deena Beneda Khosh,‖ Jeanne Drisko,‖ and Mark Levine*‡ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2516281/*

Antioxidant intake from diet and supplements and risk of digestive cancers in middle-aged adults: results from the prospective NutriNet-Santé cohort.

"Healthcare professionals may promote intake of these antioxidants in healthy amounts in order to reduce the incidence of this type of malignancy."

Study Abstract

The results of the study showed that increased dietary levels of antioxidants such as vitamin C, E, β-carotene, and selenium are associated with lower risk of developing colon cancer. This important study has demonstrated the link between antioxidants and digestive cancer risk. The harmful effects of alcohol and smoking are also apparently reduced by the intake of selenium and vitamin E, respectively. Overall, antioxidants in the diet may reduce the risk of developing gastrointestinal cancers. Healthcare professionals may promote intake of these antioxidants in healthy amounts in order to reduce the incidence of this type of malignancy.

https://www.ncbi.nlm.nih.gov/pubmed/28927476

Antioxidant intake from diet and supplements and risk of digestive cancers in middle-aged adults: results from the prospective NutriNet-Santé cohort. Egnell, M., et al. (2017). British Journal of Nutrition. doi:10.1017/S0007114517002392

Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration.

Linus Pauling and his associate, Ewan Cameron, MD, did not claim that vitamin C cured cancer, only that it extended lives making the patient feel better. This Korean study supports the Pauling /Cameron claim of longer and better lives for terminal cancer patients.

Study Abstract

Over the years there has been a great deal of controversy on the effect of vitamin C on cancer. To investigate the effects of vitamin C on cancer patients' health-related quality of life, we prospectively studied 39 terminal cancer patients. All patients were given an intravenous administration of 10 g vitamin C twice with a 3-day interval and an oral intake of 4 g vitamin C daily for a week. And then we investigated demographic data and assessed changes in patients' quality of life after administration of vitamin C. Quality of life was assessed with EORTC QLQ-C30. In the global health/quality of life scale, health score improved from 36+/-18 to 55+/-16 after administration of vitamin C ($p=0.001$). In functional scale, the patients reported significantly higher scores for physical, role, emotional, and cognitive function after administration of vitamin C ($p<0.05$). In symptom scale, the patients reported significantly lower scores for fatigue, nausea/vomiting, pain, and appetite loss after administration of vitamin C ($p<0.005$). The other function and symptom scales were not significantly changed after administration of vitamin C. In terminal cancer patients, the quality of life is as important as cure. Although there is still controversy regarding anticancer effects of vitamin C, the use of vitamin C is considered a safe and effective therapy to improve the quality of life of terminal cancer patients.

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Changes of terminal cancer patients' health-related quality of life after high dose vitamin C administration. Yeom CH1, Jung GC, Song KJ. J Korean Med Sci. 2007 Feb;22(1):7-11.

Vitamin C - a new player in regulation of the cancer epigenome.

Study Abstract

Over the past few years it has become clear that vitamin C, as a provider of reduced iron, is an essential factor for the function of epigenetic regulators that initiate the demethylation of DNA and histones. **Vitamin C deficiency is rare in the general population, but is frequently observed in patients with cancer**. Genes encoding epigenetic regulators are often mutated in cancer, underscoring their central roles in carcinogenesis. In hematological cancers, such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), drugs that reverse epigenetic aberrations are now the standard of care. Recent in vitro studies suggest that vitamin C at physiological concentrations, combined with hypomethylating agents may act synergistically to cause DNA demethylation through active and passive mechanisms, respectively. Additionally, several recent studies have renewed interest in the use of pharmacological doses of vitamin C injected intravenously to selectively kill tumour cells. This review will focus on the potential of vitamin C to optimize the outcome of epigenetic therapy in cancer patients and alternatively to act as a therapeutic at high doses.

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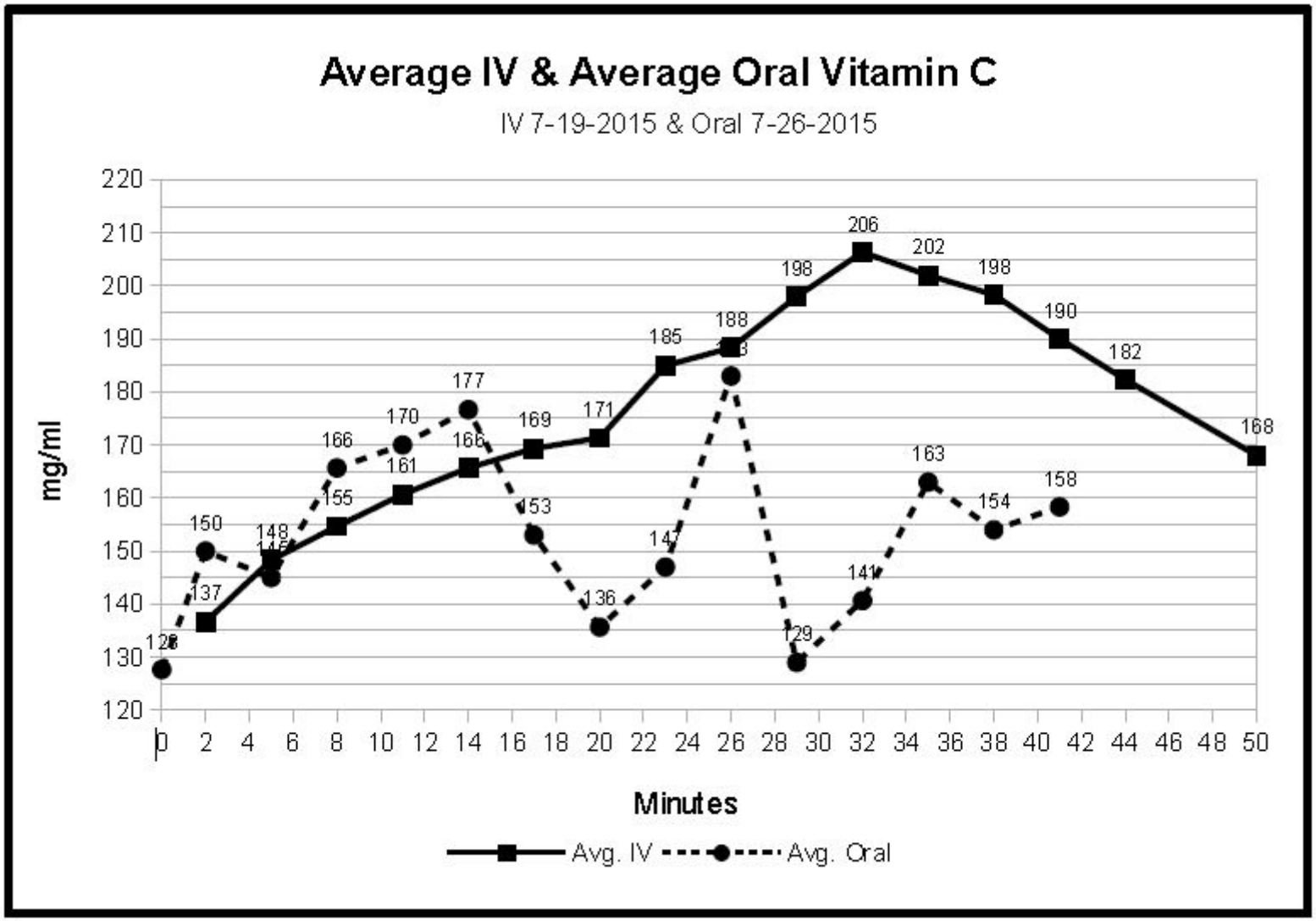
Vitamin C - a new player in regulation of the cancer epigenome. Semin Cancer Biol. 2017 Nov 1. pii: S1044-579X(17)30189-X. doi:10.1016/j.semcancer.2017.11.001. [Epub ahead of print] Gillberg L1, Ørskov AD1, Liu M2, Harsløf LBS3, Jones PA2, Grønbæk K4.

Unexpected Early Response in Oral Bioavailability of Vitamin C



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24W500 Maple Ave Suite 107 Naperville IL 60540
OwenFonorow@inteligentVitaminC.com

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