

# **Arginine: Friend or Foe in Nutrition Support for People with Cancer**

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## **Introduction**

Arginine is one of the 20 amino acids found in protein with numerous roles in cellular metabolism. It is nonessential (dispensable) in healthy people because it can be synthesized from other amino acids. However, in people who are seriously ill or injured, arginine requirements are elevated, and the body may be unable to synthesize a sufficient amount to meet needs.<sup>1</sup> Thus, arginine is considered to be conditionally essential, or conditionally indispensable and supplementation may be necessary.<sup>2-3</sup> Research that examines the benefits of arginine in people with cancer spans the over the last 20 years and has shown very positive results with immune response, wound healing, length of stay, and infection rate. Arginine has been shown to have important functions that play a role in these benefits, including:

- Promotion of protein/collagen synthesis<sup>3</sup>
- Promotion of wound healing<sup>2-3</sup>
- Support of the immune system<sup>3-6</sup>

Arginine and Protein Synthesis/Wound Healing. A number of stressors, including acute and chronic wounds, can increase the body's need for arginine. The result is that arginine availability for generation of new tissue is limited.<sup>2-3</sup> Arginine is important in healing because it is a precursor of substances and/or a regulator of processes required for tissue regeneration. Research shows that supplemental arginine significantly increases the amount of hydroxyproline—a precursor of collagen—deposited in an experimental wound.<sup>3</sup> Also,

some immune cells such as macrophages secrete a hormone-like substance called nitric oxide (NO), which is derived from arginine. NO works primarily by destroying microorganisms and/or serving as a signaling agent to promote immune response at the site of an injury or wound. In addition to being a signaling agent, NO also plays a role in blood pressure regulation, neurotransmission, angiogenesis, and apoptosis.<sup>7</sup> NO production is helpful in healing because it causes nearby blood vessels to dilate, thus promoting oxygenation of tissues, an essential process for progression of wound resolution.<sup>8</sup> Therefore, there are a number of reasons to believe that arginine can have a positive effect on hard to heal wounds.

Arginine and Immune Response. Animal research has shown that supplementing the diet with arginine increases T-lymphocyte count as measured by weight of the thymus gland.<sup>2-3,5-6</sup> Lymphocytes are white blood cells that coordinate immune activity and T-lymphocytes are those that reach “maturity” in the thymus. Human studies also show that supplemental arginine can increase not only the number of lymphocytes but also the lymphocyte response to immune system stimulation.<sup>9</sup>

The relationship between arginine and immune response also has implications for cancer therapy. A series of animal and cell culture studies have shown that arginine may influence tumor activity, size, and regression, as well as increased immune response, as shown by a proliferation of lymphocytes. The increase in immune response has been shown to correlate with an increased period of tumor inactivity, reduced tumor size, and **shortened time to tumor regression**. Human studies of arginine in patients with cancer have shown positive effects on the immune response, wound healing, length of stay, and infection rate. These studies will be reviewed in more detail later in this article.

## **Arginine Metabolism, Utilization and Transport in Cells**

Humans derive arginine via synthesis from citrulline in the liver and from the diet. Arginine taken by mouth is absorbed from the small intestine and is taken up by many cells through an active transport system. Cancer patients with weight loss have a lower plasma concentration of arginine than well-nourished or malnourished people without cancer in the fasting state<sup>10-12</sup>, suggesting that decreased arginine availability is a feature of the presence of cancer.

Disturbances in arginine metabolism possibly contribute to events that lead to cancer cachexia. Some studies indicate that animals with tumors have an increased demand for arginine.<sup>13-14</sup> **Further, inadequate intake of arginine does not up-regulate synthesis of arginine, and in patients with or without cancer, plasma arginine levels are not raised in response to feeding.<sup>10</sup> These studies collectively indicate that even in the face of low plasma levels of arginine, the stressed body may not compensate by increasing production of it.**

Arginine transport is highly regulated and can be affected by a variety of stimuli, including cytokines and other inflammatory stimuli. The net beneficial or negative effect of how arginine is metabolized depends upon the strength of the activities of each of these arginine-catabolizing enzymes. Understanding how these enzymes are regulated in vivo will help us to apply the use of arginine in health and disease.

Two critical pathways for arginine. Activity or expression of the nitric oxide synthase (NOS) and arginase isozymes represent the most important regulated changes in arginine metabolism. The arginase isozymes hydrolyze arginine to urea and ornithine mainly in the liver, and are stimulated by T helper-2 (Th2) cytokines (interleukin-4 and -13, transforming

growth factor- $\beta$  and prostaglandin E2).<sup>15</sup> Therefore, cancer and the environment it creates can affect arginine metabolism of the host. A delicate balance exists as to whether arginine will be used to produce nitric oxide or whether it will be broken down to urea and ornithine (a precursor for polyamines, needed for growth of cells) in the kidney.<sup>15</sup>

The majority of nitric oxide is formed from arginine (via the NOS isozyme, iNOS) in almost all cell types following stimulation from T helper-1 (Th1) cytokines (interleukin-1 and -12, tumor necrosis factor-alpha and gamma-interferon).<sup>16</sup> The complexities that orchestrate activation of arginine enzymes are important for understanding how arginine use is misunderstood and controversial in cancer. The overall biological effect of the production of NO depends on several factors including its concentration, when it is expressed, the cell that produced it and its target cell. In addition, the surrounding environment can influence NO activity through its interaction with reactive oxygen species, metal ions, and proteins.<sup>15</sup> In other words, it is over-simplified and incorrect to say that dietary arginine feeds a tumor.

### **Arginine and Cancer: Animal Studies**

It is becoming widely recognized that the response of tumors to arginine depletion or supplementation is dependent on tumor type and immunogenicity (ability to induce humoral and/or cell-mediated immune responses) of the tumor. The mechanism(s) by which arginine can modulate tumor metabolism are multifactorial. The two most important mechanisms appear to be as:

- a metabolic precursor for production of polyamines
- the precursor for NO

As stated previously, NO is involved in a wide array of physiological processes. However, it is cell-mediated immunity which seems to be the primary determinant in how a tumor responds to arginine. Cell culture studies have shown that macrophages metabolize arginine to NO during tumor rejection, whereas macrophage arginine metabolism *via* arginase results in local production of polyamines during periods of progressive tumor growth.<sup>17</sup>

In animal tumor models, supplemental arginine has been shown to have an effect on antitumor mechanisms, slowed tumor growth, and prolonged survival.<sup>18</sup> In one study of a mouse model, parenteral arginine supplementation stimulated tumor growth in a weakly immunogenic colon tumor metastatic to the liver and arginine depletion inhibited growth of the same metastatic tumor.<sup>19</sup> Only animal studies of parenteral delivery of arginine have shown stimulation of tumor growth.<sup>20</sup> However, it is interesting to note that even the parenteral studies are not equivocal, and that some have shown that arginine inhibits tumor growth.<sup>21</sup>

Many other animal studies have been published which demonstrate inhibition of tumor growth by supplemental dietary arginine. Recent reports showing that arginine inhibits tumor growth include a study of chemically induced colorectal cancer and Walker 256 carcinosarcoma in rats.<sup>21-22</sup> While the collection of published animal studies is too large to include here in entirety, the key take away is that whether arginine enhances or inhibits tumor growth depends on suppression of the immune system. While the studies are very interesting, we need to take caution with mechanistic research. The overall impact of cancer on how the human body metabolizes amino acids depends upon the tumor size. In cell or animal studies, the amount of burden that the tumor has on the system is relatively large

compared to the size/burden of the tumor in humans. Therefore, caution needs to be taken when interpreting and applying findings from animal studies to the clinical setting.

## **Arginine and Cancer: Human Studies**

A review of the literature was undertaken to find studies investigating arginine or arginine-containing nutritional products and their effects on people with cancer. None of the studies examine tumor growth, and for the most part explore infection rates, wound healing, immune system function, survival, and markers of nutritional status. Many of the studies focus on surgical patients, although some examine the use of arginine or arginine-containing nutritional products as adjunctive treatment either in building lean body mass or as an enhancement to chemotherapy. All of the studies examine oral supplementation, except for one that investigated parenteral arginine. (The review resulted in 17 papers which are listed in order of publication date in Table 1).

Three early studies showed positive clinical response to chemotherapy in patients with breast tumors when patients consumed 30 grams of arginine for 3 days prior to therapy.<sup>23-26</sup> The aim of these studies was to see if arginine could augment specific chemotherapeutic regimens by increasing the rate of protein synthesis in the tumor, not to examine whether or not arginine causes tumor growth. Results showed that the rate of protein synthesis in the tumor was enhanced, potentially improving the response to cell-cycle-specific chemotherapeutic agents.<sup>25-26</sup> In one of the studies, subjects who consumed arginine had a 95% response rate to the chemotherapy which is higher than the rate documented in previous reports of patients treated with the same chemotherapeutic regimen.<sup>26</sup> Park proposes that this offers a possibility for using elevated levels of dietary arginine as an adjuvant to chemotherapy.<sup>25</sup>

Two longer-term, lower dose studies were conducted in head and neck cancer and gastric cancer in the perioperative time frame. Although standard nutritional product performed better than an arginine-containing formula in QOL measures in head and neck cancer, this study showed no adverse effects of the arginine-containing product on survival over 6 months.<sup>27</sup> A 16-week study in gastric cancer showed that subjects who received an arginine-containing product fared better in rate of re-hospitalization than those who had a standard formula.<sup>28</sup>

There are several other studies that examined the use of an arginine-containing immunonutrition product in the perioperative period. One study showed reduction in duration of post-operative systemic inflammatory response syndrome (SIRS) in esophagectomy patients.<sup>29</sup> In another study of head and neck cancer patients, those supplemented with 12.5 gm arginine had a trend for better survival than those not supplemented with arginine. In addition, supplementation with arginine did not negatively affect clinical outcomes.<sup>30</sup>

Several studies have investigated the use of arginine-containing immunonutrition in the post-operative period.<sup>31-35</sup> Two studies showed decreased rate of fistula formation<sup>34,36</sup>, and others showed reduction in wound complications (including infection) and increased hydroxyproline content (a marker of healing) at the wound site.<sup>31,33,36</sup> In a study of parenteral nutrition, colorectal cancer patients either received or did not receive 20g arginine/day for 7 days post-operatively. Patients were immune suppressed before operation, and the condition was improved only in the arginine group at days 4 and 7 (P<0.05). The authors concluded

that arginine can improve **immune function in patients with colorectal cancer after surgery**.<sup>37</sup>

Two studies examined the effect of a mixture of amino acids (including 14g of arginine/day for up to 24 weeks) on lean mass accretion in advanced cancer patients with solid tumors.<sup>38-39</sup> One study showed a trend in improvement in prealbumin and a significant increase in lean body mass in the group that consumed the mixture with arginine.<sup>38</sup> The other study showed a positive trend toward increase in lean body mass with the arginine mixture.<sup>39</sup> Neither of the studies reported adverse events or decreased survival with the use of an arginine-containing product.

## **Enzymatic Arginine Deprivation as Treatment**

Certain cancers may be auxotrophic (auxotrophy is the inability of an organism to synthesize a product required for its growth) for a particular amino acid, and amino acid deprivation is one method to treat these tumors. Several mouse and human melanomas are unable to synthesize arginine. Therefore, it has been suggested that an arginine-degrading enzyme may prove effective in controlling arginine-requiring cancers.<sup>40</sup>

Enzymatic arginine deprivation is a novel approach to target tumors which lack argininosuccinate synthetase (ASS) expression. ASS is a key enzyme which converts citrulline to arginine. Tumors which usually do not express ASS include hepatocellular carcinoma, some mesotheliomas and some renal cell cancers. Arginine can be degraded by several enzymes including arginine deiminase (ADI). ADI has high affinity to arginine and catalyzes arginine to citrulline and ammonia. Citrulline can be recycled back to arginine in normal cells which express ASS, whereas ASS(-) tumor cells cannot. A pegylated form of

ADI (ADI-PEG20) has been formulated and has shown in vitro and in vivo activity against melanoma, hepatocellular carcinoma, and some renal cell cancers.<sup>40</sup> Phase I and II clinical trials with ADI-PEG20 have been conducted in patients with melanoma<sup>41</sup> and hepatocellular carcinoma<sup>42</sup>, and antitumor activity has been demonstrated in both cancers. One criticism of these studies is that they are underpowered. For instance, the melanoma study included 39 subjects.<sup>41</sup> These trials did not examine the role of dietary intake of arginine or amino acids that are precursors to arginine.

What does the literature show about dietary arginine deprivation? Only one study of dietary arginine deprivation in mice resulted in a reduced number of tumors and tumor incidence.<sup>43</sup> However, the tumor reduction effect was completely reversed when the animals were fed ornithine.<sup>43</sup> Data to suggest that dietary arginine counteracts pharmaceutical tumor enzymatic arginine deprivation does not exist in humans. In the human diet, it would be very difficult to advise arginine and ornithine deprivation.

Collectively, the effectiveness of enzymatic arginine deprivation in some tumors remains to be determined until larger clinical trials are conducted. Even if the effectiveness of this type of treatment is proven, the possible confounding effect of dietary arginine and other amino acids that are precursors of arginine will require extensive investigation. Until these questions are answered, it is not wise to draw any conclusive clinical or nutritional recommendations.

## **Arginine Supplementation as Nutrition Support**

In certain cases, arginine supplementation may be beneficial in managing the nutritional therapy of a patient with cancer. Managing wounds is complicated by cancer, comorbidities (eg., diabetes, renal disease), and the detrimental effect that the tumor has on the body. In addition, the treatments for cancer are complex and multi-faceted (eg., surgery, radiation, and chemotherapy) and can have a profound effect on wound healing and/or the development of wounds. Supplemental arginine may also play a role in building lean body mass in people with cancer<sup>38-39</sup> as some data show evidence that cancer patients are arginine deficient and could lead to metabolic events that ultimately result in cachexia.<sup>44</sup> Fifty to ninety percent of patients with cancer lose weight and/or lean body mass during the course of their disease.<sup>45</sup>

Understanding the healing process and nutritional influences on wound outcome is critical to successful nutritional management of the wound patient. Wounds require protein to heal and if the diet is inadequate, the amino acids needed are drawn from lean body mass- muscle and vital organs. Amino acids in the body make up functional proteins and are not “stored” like some other nutrients. Utilizing even a small amount of lean mass for energy results in loss of ability to heal, organ function, immune response, and mobility. Muscles, organs, the tumor, and the healing wound compete for a steady supply of amino acids to serve as building blocks for the synthesis of new tissue and typically, the tumor or the organs and muscles win that competition.<sup>46</sup>

Radiotherapy can lead to injury. Radiotherapy can have profound effects, both immediate and long-term, on the skin and connective tissue. Radiotherapy also affects the time course and end result of wound healing and the risk of postoperative complications. The energy

transfer from the radiation generates highly reactive chemical products which combine with normal body components that in the end cause cellular damage. The cells that are most affected by radiation damage are cells that are rapidly dividing, including cells of the skin, bone marrow and GI tract.<sup>47-49</sup>

Healing is critical after surgery. Timing of surgery is important in relationship to radiotherapy and risk of non-healing wounds. Fewer wound complications have been demonstrated when postoperative radiotherapy is selected. Because radiation exposure delays wound healing due to effects on the skin, connective tissue and blood vessels, it makes sense that the surgical wound should be healed before initiation of radiotherapy. If the surgical wound is not healed or is not completely healed and radiotherapy is initiated, further wound complications may arise. Typically, clinicians wait three weeks post-surgery for complete healing. However, if there is a surgical site infection, initiation of radiotherapy may be delayed for several weeks. Benefits of radiotherapy may decrease if it is delayed more than 6 to 8 weeks postoperatively.<sup>48-49</sup>

Chemotherapy can interfere with wound healing. Overall, chemotherapeutic agents cause symptoms on various organ systems within the body, and generally effect cells that grow and reproduce rapidly. Since the skin and epithelial cells grow and divide rapidly, there may be a detrimental effect on ability to heal in a normal manner. There are several approaches that can be taken by oncology care providers, including the delay of chemotherapy of 7 to 10 days postoperatively in order to reduce effects on wound healing.<sup>49</sup>

## **Summary**

Arginine is a conditionally-essential amino acid; it is made by the body in sufficient quantities under usual conditions, but a dietary source becomes necessary during periods of

stress or healing.<sup>1</sup> Arginine has been shown to have several important benefits, including promotion of protein/collagen synthesis, wound healing and support of the immune system.<sup>2-6,9</sup> Although dietary arginine deprivation has been shown in a mouse model to reduce the number of tumors and tumor incidence<sup>43</sup>, human data have not shown that dietary arginine enhances tumor growth, decreases survival or hastens tumor progression. On the contrary, arginine supplementation has been studied in a variety of cancer types in humans, and positive results have been seen with immune response, wound healing, length of stay, and infection rate.<sup>24-39</sup> Cancer patients recovering from surgery, radiation-induced injury, or who have wounds that are resistant to healing may benefit from a nutritional regimen that includes a source of arginine.

## **References**

1. Barbul A, Sisto DA, Wasserkrug HL et al. Nitrogen sparing and immune mechanisms of arginine: Differential dose-dependent responses during postinjury intravenous hyperalimentation. *Curr Surg*. 1963;40:114-116.
2. Barbul A, Lazarow SA, Efrom DT, et al. Arginine enhances wound healing and lymphocyte immune responses in humans. *Surgery*. 1990;108:331-337.
3. Kirk SJ, Hurson M, Regan MC et al. Arginine stimulates wound healing and immune function in elderly human beings. *Surgery* 1993;114:55–160.
4. Barbul A, Fishel RS, Shimazu S, et al. Intravenous hyperalimentation with high arginine levels improves wound healing and immune function. *J Surg Res*. 1985;38:328-334.
5. Barbul A, Sisto DA, Wasserkrug HL, Efron G. Arginine stimulates lymphocyte immune response in healthy human beings. *Surgery*. 1981;90:244-251.
6. Barbul A, Wasserkrug HL, Sisto DA, et al. Thymic stimulatory actions of arginine. *J Parenter Enteral Nutr*. 1980;4:446-449.
7. Nathan CA. Nitric oxide as a secretory product of mammalian cells. *FASEB J*. 1992;6:3051-3064.
8. Alexandrova R, Mileva M, Zvetkova E. Nitric oxide and cancer. *Exp Pathology Parasitology*. 2001;4:13-18.
9. Barbul A, Wasserkrug HL, Sisto DA et al. Thymic stimulatory actions of arginine. *JPEN*. 1980;4:446-449.

10. Bennegard K, Lindmark L, Eden E, et al. Flux of amino acids across the leg in weight-losing cancer patients. *Cancer Res.* 1984;44:386-393.
11. De Blaauw I, Heeneman S, Deutz NEP, Von Meyenfeldt MF. Increased whole-body protein and glutamine turnover in advanced cancer is not matched by an increased muscle protein and glutamine turnover. *J Surg Res.* 1997;68:44-55.
12. Norton JA, Gorschboth CM, Wesley Ra, et al. Fasting plasma amino acid levels in cancer patients. *Cancer.* 1985;56:1181-1186.
13. Marquez J, Mates JM, Quesada AR, et al. Altered ornithine metabolism in tumor-bearing mice. *Life Sci* 1989;45:1877-1884.
14. Easson AM, Pawlik TM, Fischer CP, et al. Tumor-influenced amino acid transport activities in zonal-enriched hepatocyte populations. *Am J Physiol* 2000;279:G1209-G1218.
15. Lind SD. Arginine and cancer. *J Nutr.* 2004;134:2837S-2841S.
16. Bansal V and Ochoa JB. Arginine availability, arginase, and the immune response *Curr Opin Clin Nutr Metab Care.* 2003 Mar;6(2):223-8.
17. Mills CD, Shearer J, Evans R, and Caldwell MD. Macrophage arginine metabolism and the inhibition of cancer. *J. Immunol.* 1992;149:2709-2714.
18. Daly JM, Lieberman MD, Goldfine J, et al., Enteral nutrition supplemented with arginine, RNA and omega-3 fatty acids in patients after operation; immunologic, metabolic and clinical outcome. *Surgery*;112:56-67, 1992.
19. Yeatman TJ, Risley GL, and Brunson ME. Depletion of dietary arginine inhibits growth of metastatic tumor. *Arch. Surg.* 1991;126:1376-1382.
20. Grossie VB. Citrulline and arginine increase the growth of the ward colon tumor in parenterally fed rats. *Nutr Cancer.* 1996;26:91-97.

21. Ye SL, Istfan NW, Driscoll DF and Bistran BR. Tumor and host response to arginine and branched chain amino acid-enriched total parenteral nutrition. *Cancer*. 1992;69:261-270.
22. Ma Q, Hoper M, Anderson N, and Rowlands BJ. Effect of supplemental L-arginine in a chemical-induced model of colorectal cancer. *World J. Surgery*. 1996;20:1087-1091.
23. Park KGM, Heys SD, Blessing K, et al. Stimulation of human breast cancers by dietary L-arginine. *Clin. Science*. 1992;82:413-417.
24. Brittenden J, Heys SD, Miller I, et al. Dietary supplementation with L-arginine in patients with breast cancer (>4cm) receiving multimodality treatment: report of a feasibility study. *Br J Cancer* 1994;69:918-921.
25. Heys SD, Ogston K, Miller I, et al. Potentiation of the response to chemotherapy in patients with breast cancer by dietary supplementation with L-arginine: results of a randomized controlled trial *Int J Oncol*. 1998 Jan;12(1):221-5.
26. Brittenden J, Park KG, Heys SD, et al. L-arginine stimulates host defenses in patients with breast cancer *Surgery* 1994;115:205-212.
27. van Bokhorst-de Van der Schuer MA, Langendoen SI, Vondeling H, et al. Perioperative enteral nutrition and quality of life of severely malnourished head and neck cancer patients: a randomized clinical trial. *Clin Nutr*. 2000 Dec;19(6):437-44.
28. Daly JA, Weintraub FN, Shou J, et al. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. *Ann Surg*. 1995 Apr;221(4):327-38.
29. Takeuchi H, Ikeuchi S, Kawaguchi Y, et al. Clinical significance of perioperative immunonutrition for patients with esophageal cancer. *World J Surg* 2007 Nov; 31(11):2160-2167.

30. van Bokhorst-De Van Der Schueren MA, Quak JJ, von Blomberg-van der Flier BME, et al. Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function, postoperative morbidity, and survival in severely malnourished head and neck cancer patients. *Am J Clin Nutr.*, 2001 Feb;73(2):323-32.
31. Farreras N, Artigas V, Cardona D, et al. Effect of early postoperative enteral immunonutrition on wound healing in patients undergoing surgery for gastric cancer. *Clin Nutr.* 2005 Feb;24(1):55-65.
32. Chen DW, Wei Fei Z, Zhang YC, et al. Role of enteral immunonutrition in patients with gastric carcinoma undergoing major surgery. *Asian J Surg.* 2005 Apr;28(2):121-124.
33. de Luis DA, Aller R, Izaola O, et al. Postsurgery enteral nutrition in head and neck cancer patients. *Eur J Clin Nutr.* 2002 Nov;56(11):1126-1129.
34. de Luis DA, Izaola O, Aller R, et al. A randomized clinical trial with oral Immunonutrition (omega3-enhanced formula vs. arginine-enhanced formula) in ambulatory head and neck cancer patients. *Ann Nutr Metab* 2005 Mar-Apr;49(2):95-99.
35. de Luis DA Izaola O, Cuellar L, et al. Clinical and biochemical outcomes after a randomized trial with a high dose of enteral arginine formula in postsurgical head and neck cancer patients. *Eur J Clin Nutr.* 2007 Feb;61(2):200-204.
36. Casas-Rodera P, Gomez-Candela C, Benitez S, et al. Immunoenhanced enteral nutrition formulas in head and neck cancer surgery: a prospective, randomized clinical trial. *Nutr Hosp.* 2008 Mar-Apr;23(2):105-110.

37. Song JX, Qing SH, Huang XC, and Qi DL, et al. Effect of parenteral nutrition with L-arginine supplementation on post-operative immune function in patients with colorectal cancer *Di Yi Jun Yi Da Xue Xue Bao*. 2002 Jun;22(6):545-547.
38. May PE, Barber A, D'Olimpio JT, et al. Reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine. *Am J Surg* 2002;183:471-479.
39. Berk L, James J, Schwartz A, et al. A randomized, double-blind placebo controlled trial of beta-hydroxy-beta-methylbutyrate, glutamine, and arginine mixture for the treatment of cancer cachexia (RTOG 0122). *Support Care Cancer*. 2008;16:1179-1188.
40. Feun L, You M, Wu CJ et al. Arginine deprivation as targeted therapy for cancer. *Curr Pharm Des*. 2008;14:1049-1057.
41. Ascierto PA, Scala S, Castello A, et al. Pegylated arginine deiminase treatment of patients with metastatic melanoma: Results from phase I and II studies. *J Clin Oncol*. 2005;23:7660-7668.
42. Lam TL, Wong GK, Chong HC et al. Recombinant human arginase inhibits proliferation of human hepatocellular carcinoma by inducing cell cycle arrest. *Cancer Lett* 2009 Jan 10 Epub ahead of print.
43. Gonzalez GG and Byus CV. Effect of dietary arginine restriction upon ornithine and polyamine metabolism during a two-stage epidermal carcinogenesis in the mouse. *Cancer Res*. 1991;51:2932-2939.
44. Vissers YLJ, Dejong CHC, Luiking YC, et al. Plasma arginine concentrations are reduced in cancer patients: evidence for arginine deficiency? *Am J Clin Nutr*. 2005;81:1142-1146.

45. De Wys WD, Begg C, Lavin PT, et al. Prognostic effects of weight loss prior to chemotherapy in cancer patients. *Am J Med.* 1980;69:491-497.
46. Wolfe R. The underappreciated role of muscle in health and disease. *Am J Clin Nutr* 2006;84:475-482.
47. Mendelsohn FA, Divino CM, Reis ED, and Kerstein MD. Wound care after radiation therapy. *Adv Skin Wound Care.* 2002;216:218-224.
48. Wang J, Boerma M, Fu Q, and Hauer-Jensen H. Radiation responses in skin and connective tissues: effect on wound healing and surgical outcome. *Hernia* 2006;10:502-506.
49. Payne WG, Naidu DK, Wheeler CK, et al. Wound healing in patients with cancer. *ePlasty.* January 11, 2008; 8:68-90.

Human Studies of Arginine Supplementation in Cancer Patients				
Citation	Objective	Design	Results	Authors' Conclusions
Park, K et al. Stimulation of human breast cancers by dietary L-arginine. <i>Clinical Science</i> 1992;82:413-417.	To determine the effects of L-arginine on protein synthesis in human breast tumors	-Prospective, randomized, controlled clinical trial -20 pts with breast cancer -Randomized to receive either 30 g of L-arginine or placebo for 3 days prior to surgery -Rate of tumor protein synthesis was measured by incorporation of stable isotope (C-leucine) into tumor protein	Median rate of tumor protein synthesis was 10%/day in placebo group; 25%/day in arginine group (p<0.005)	“Arginine stimulates protein synthesis in human tumors <i>in vivo</i> . This provides a potentially important means of therapeutically modulating tumors, not by inhibiting growth, but by stimulating tumor cell turnover and sensitizing these cancers to cell-cycle-specific chemotherapeutic agents”
Brittenden J et al. Dietary supplementation with L-arginine in patients with breast cancer	To evaluate the feasibility of using L-arginine, in combination	-Phase II pilot study -44 pts with breast cancer received 30 g	Following the treatment, 95% of pts had a clinical response: 30%	“Clinical response rates obtained following L-arginine and

<p>(&gt;4cm) receiving multimodality treatment: report of a feasibility study. <i>Br J Cancer</i> 1994;69:918-921.</p>	<p>with primary chemotherapy, in the management of pts with large breast tumors</p>	<p>of L-arginine for 3 days prior to each cycle of CHOP (vincristine, cyclophosphamide, doxorubicin) therapy followed by 4-6 cycles of radiotherapy</p>	<p>had complete response, 65% had partial response</p>	<p>CHOP chemotherapy were higher than those documented in previous reports of pts treated with the same chemotherapeutic regimen. L-arginine was well-tolerated and did not appear to increase the side-effects of chemotherapy.”</p>
<p>Brittenden J et al. L-arginine stimulates host defenses in patients with breast cancer <i>Surgery</i> 1994;115:205-212.</p>	<p>To examine the effect of host defenses in patients with breast cancer.</p>	<p>-Single-arm trial -Patients with locally advanced breast cancer -Given a standard diet supplemented with 30 grams L-arginine for 3 days</p>	<p>Lymphocyte responses to mitogens, NK and LAK cell cytotoxic activities all increased, but no increase in numbers of CD16-positive (NK) or CD56-positive (LAK) cell numbers after L-arginine supplementation.</p>	<p>“L-arginine in patients with breast cancer significantly enhances host defenses and therefore may have a role in adjuvant treatment.”</p>

<p><i>Daly JA et al. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. Ann Surg. 1995 Apr;221(4):327-38</i></p>	<p>To evaluate long-term enteral nutrition support in postoperative cancer patients</p>	<p>-Prospective, randomized, controlled clinical trial          -Sixty adult patients with esophageal, gastric, and pancreatic lesions          -Randomized to receive arginine, RNA + omega-3 fatty acid diet or standard diet          -Beginning on the first postoperative day until hospital discharge.          -Also were randomized to receive or not receive enteral feedings for the 12- to 16-week recovery and radiation/chemo periods</p>	<p>Infectious/wound complications occurred in 10% of the arginine, RNA + omega-3 fatty acid group compared with 43% of the standard group (p &lt; 0.05); mean length of hospital stay was 16 vs. 22 (p &lt; 0.05) days, respectively.</p>	<p>“Supplemental enteral feeding with arginine, RNA + omega-3 fatty acids significantly increased plasma and peripheral white blood cell omega-3/omega-6 ratios and significantly decreased PGE<sub>2</sub> production, and postoperative infectious/wound complications compared with standard feeding. For outpatients receiving adjuvant therapy, those initially randomized to oral feedings alone required rehospitalization more frequently, and 61% crossed over to supplemental enteral feedings.”</p>
<p>Heys SD, et al. Dietary supplementation with L-arginine: modulation</p>	<p>To determine what effect dietary</p>	<p>-Prospective, randomized, controlled</p>	<p>Tumors from patients receiving L-</p>	<p>“These findings confirm the</p>

<p>of tumour-infiltrating lymphocytes in patients with colorectal cancer. <i>Br J Surg</i> 1997;84:238-241.</p>	<p>supplementation with L-arginine (30g/day for 3 days) has on tumor-infiltrating lymphocytes (TILs) in patients with colorectal cancer.</p>	<p>clinical trial -18 patients with colorectal cancer -Received either a standard hospital diet or a standard diet supplemented with 30 g L-arginine for 3 days prior to surgery</p>	<p>arginine contained increased numbers of specific cell subsets (CD16 and CD56 surface markers) of TILs, specifically NK (natural killer) and LAK (lymphokine-activated killer) cells.</p>	<p>potential powerful therapeutic effects of dietary manipulation and have implications for the immunotherapeutic treatment of malignant disease in humans.”</p>
<p>Heys SD, et al. Potentiation of the response to chemotherapy in patients with breast cancer by dietary supplementation with L-arginine: results of a randomized controlled trial <i>Int J Oncol.</i> 1998 Jan;12(1):221-5.</p>	<p>To determine if L-arginine is beneficial to pts with breast cancer undergoing neo-adjuvant chemotherapy</p>	<p>-Prospective, randomized, controlled clinical trial -96 breast cancer pts -Randomized to receive 30 gms L-arginine for 3 days or placebo prior to undergoing CHOP therapy</p>	<p>Clinical response in the L-arginine group was 77% (23% complete and 54% partial responses) compared to 71% (15% complete and 56% partial) in the placebo (p=ns).</p>	<p>“In patients with tumors less than 6 cm in initial diameter, there was a significant increase in the better histopathological responses in the L-arginine group compared with placebo (88% vs 52%, p=0.04). This may have important implications for clinical practice.”</p>

<p><i>Van Bokhorst-de Van der Schuer MA et al. Perioperative enteral nutrition and quality of life of severely malnourished head and neck cancer patients: a randomized clinical trial. Clin Nutr. 2000 Dec;19(6):437-44</i></p>	<p>To evaluate the use of perioperative nutritional support on Quality of Life (QOL) in malnourished head and neck cancer patients undergoing surgery</p>	<p>-Prospective, randomized, controlled clinical trial -49 malnourished head and neck cancer patients -Randomized to receive either no preoperative and standard postoperative tube-feeding (group I), standard preoperative and postoperative tube-feeding (group II) or arginine-supplemented preoperative and postoperative tube-feeding (group III) -Groups I and II were blinded</p>	<p>Between baseline and the day before surgery, both preoperatively fed groups revealed a positive change for the dimensions physical and emotional functioning and dyspnea (with significance in group II, P=0.050,0.031, 0.045 respectively). Group III showed a negative change in appetite (P=0.049). Between baseline and 6 months after surgery, there were no differences between group I and both pre-fed groups. There were no differences in favour of group III compared to group II</p>	<p>“Enteral nutrition improves QOL of severely malnourished head and neck cancer patients in the period preceding surgery. No benefit of preoperative enteral feeding on QOL could be demonstrated 6 months after surgery.”</p>
<p>van Bokhorst-De Van Der Schueren MA et al. Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function,</p>	<p>To study the effect of perioperative, arginine-supplemented nutritional support on nutritional</p>	<p>-Prospective, randomized, controlled clinical trial -49 patients were randomly assigned to receive 1) no</p>	<p>Major postoperative complications occurred in 53%,. 47%, and 59% of patients in study groups 1, 2, and 3</p>	<p>“Nine days of preoperative tube feeding, with or without arginine, did not significantly</p>

<p>postoperative morbidity, and survival in severely malnourished head and neck cancer patients. <i>Am J Clin Nutr.</i>, 2001 Feb;73(2):323-32</p>	<p>status, immune status, postoperative outcome, and survival in severely malnourished head and neck cancer patients undergoing major surgery</p>	<p>preoperative and standard postoperative tube feeding, 2) standard preoperative and postoperative tube feeding, or 3) arginine-supplemented preoperative and postoperative tube feeding -Groups 2 and 3 were blinded</p>	<p>(NS). A trend was seen toward better survival in the arginine-supplemented group (P = 0.15).</p>	<p>improve nutritional status, reduce the surgery-induced immune suppression, or affect clinical outcome in severely malnourished head and neck cancer patients. Patients supplemented with arginine-enriched nutrition tended to live longer. Some markers of immune function may distinguish patients with good or bad prognoses.”</p>
<p>Song JX, et al. Effect of parenteral nutrition with L-arginine supplementation on post-operative immune function in patients with colorectal cancer <i>Di Yi Jun Yi Da Xue Xue Bao.</i> 2002 Jun;22(6):545-547.</p>	<p>To evaluate the effects of parenteral nutrition supplemented with L-arginine on the immune function of pts with colorectal cancer after an operation.</p>	<p>-Prospective, randomized, controlled clinical trial -40 randomly chosen colorectal cancer pts -Received either standard PN or PN with 20g/d L-arginine for 7 days after surgical removal of tumor</p>	<p>Immune suppression was improved (as evidenced by increased CD4+, CD4+/CD8+, natural killer cells and interleukin-2R levels) in L-arginine group as compared with the results in the control group at days 4 and 7 (p&lt;0.05).</p>	<p>“Arginine can improve the immune function in pts with colorectal cancer after operation and enhance PN effect.”</p>

<p>de Luis DA et al. Postsurgery enteral nutrition in head and neck cancer patients. <i>Eur J Clin Nutr.</i> 2002 Nov;56(11):1126-9.</p>	<p>To investigate whether postoperative nutrition of head and neck cancer patients, using an arginine-enriched diet, could improve nutritional variables as well as clinical outcomes</p>	<p>-Prospective, randomized, controlled clinical trial -47 patients with oral and laryngeal cancer -Patients were randomly allocated to two groups: (a) patients receiving an enteral diet supplemented with arginine and fiber (group I); (b) patients receiving an isocaloric, isonitrogenous enteral formula (group II).</p>	<p>The incidences postoperative infection complications were similar (nine patients) in both groups (21.7% group I and 16.7% group II; NS). Fistula were less frequent in enriched nutrition group (0% group I and 20.8% group II; P&lt;0.05); wound infection was more frequent in group II, but without statistical difference (4.3% group I and 12.5% group II; NS). The length of postoperative stay was 22.8+/-11.8 days in the enriched group and 31.2+/-19.1 days in the control group (P=0.07).</p>	<p>“An arginine and fiber-enriched formula improves local wound complications in postoperative head and neck cancer patients.”</p>
<p>May PE et al. Reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine. <i>Am J Surg</i> 2002;183:471-479.</p>	<p>To investigate if supplementation of specific nutrient known to positively support protein</p>	<p>-Prospective, randomized, controlled clinical trial -49 patients with stage IV solid tumors -Patients were randomly assigned to</p>	<p>Patients supplemented with HMB/Arg/Glut gained 0.95 +/-0.66 kg body mass and 1.12 +/-0.68 kg; control lost 0.26 +/- 0.68 kg</p>	<p>“The mixture of HMB/Arg/Glut was effective at increasing fat-free mass of advanced (stage IV) cancer. There was no</p>

	synthesis and reduce protein breakdown will reverse the cachexia process in advanced cancer patients.	receive 3g HMB/14g arginine/14g glutamine or control for 24 weeks -Primary outcome measure was change in body mass and fat-free mass	body mass and 1.34 +/- 0.78 kg (p = 0.02)	negative effect of treatment on the incidence of adverse events or quality of life measure.”
de Luis DA, et al. A randomized clinical trial with oral Immunonutrition (omega3-enhanced formula vs. arginine-enhanced formula) in ambulatory head and neck cancer patients. <i>Ann Nutr Metab</i> 2005 Mar-Apr;49(2):95-99.	To investigate whether oral nutrition (omega3 fatty acid-enhanced diet versus an arginine-enhanced diet) could improve nutritional variables as well as clinical outcome, postoperative infectious and wound complications	-Prospective, randomized, controlled clinical trial -73 ambulatory postsurgical patients with oral and laryngeal cancer -At discharge from hospital the postsurgical head and neck cancer patients were asked to consume two units per day of either a specially designed omega3 fatty acid-enhanced supplement or an arginine-enhanced (12g/day) supplement for a 12-week period	Postoperative infectious complications were similar in both groups No local complications were detected in the surgical wound. Gastrointestinal tolerance (diarrhea and vomiting episodes) of both formulas was good	“At the dose taken, the omega3-enhanced formula improved fat mass and proteins in ambulatory postoperative head and neck cancer patients. The arginine-enhanced formula improved proteins.”

<p><i>Farreras N et al. Effect of early postoperative enteral immunonutrition on wound healing in patients undergoing surgery for gastric cancer. Clin Nutr. 2005 Feb;24(1):55-65</i></p>	<p>To assess the effect of early postoperative enteral immunonutrition on the wound healing process in patients undergoing surgery for gastric cancer</p>	<p>-Prospective, randomized, controlled clinical trial -66 patients with gastric cancer -Randomized to receive early postoperative enteral immunonutrition (arginine, omega-3 fatty acids and ribonucleic acid) or an isocaloric-isonitrogenous control.</p>	<p>Patients fed with immunonutrition showed higher local hydroxyproline levels (P=0.0018) and significantly lower episodes of surgical wound healing complications (0 vs. 8 (26.7%) P=0.005) when compared to patients fed with the control formula.</p>	<p>“Early postoperative enteral nutrition with a formula supplemented with arginine, omega 3 fatty acids and RNA increased hydroxyproline synthesis and improved surgical wound healing in patients undergoing gastrectomy for gastric cancer.”</p>
<p><i>Chen DW, et al. Role of enteral immunonutrition in patients with gastric carcinoma undergoing major surgery. Asian J Surg. 2005 Apr;28(2):121-4</i></p>	<p>To evaluate the influence of postoperative immunonutrition on immune and nutritional parameters in patients with gastric carcinoma.</p>	<p>-Prospective, randomized, controlled clinical trial -40 patients with gastric carcinoma (major surgery) -Randomly divided -On postoperative Day 2, patients in the standard nutrition group received a standard enteral formula, while those in the immunonutrition group received an enteral</p>	<p>There were no significant differences between the two groups in protein and immune parameters preoperatively and no significant differences in management perioperatively. No serious adverse effects were recorded with the two formulas. Postoperative procedures were smooth in both groups.</p>	<p>“Compared with standard enteral nutrition, immunonutrition can improve defense mechanisms and modulate inflammatory action after major elective surgery for gastric carcinoma.”</p>

		formula enriched with glutamine, arginine and omega-3 fatty acids. Nutritional support was continued for 7 days.		
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<p><i>Takeuchi H et al. Clinical significance of perioperative immunonutrition for patients with esophageal cancer. World J Surg 2007 Nov;31(11):2160-2167.</i></p>	<p>To investigate whether preoperative and/or postoperative enteral immune-enhanced formulas that are supplemented with arginine, omega-3 fatty acids, and RNA may reduce postoperative complications in patients undergoing esophagectomy for thoracic esophageal squamous cell carcinoma</p>	<p>-Prospective, randomized, controlled clinical trial -40 patients who underwent esophagectomy received one of 3 treatments: control enteral diet after surgery (A); enteral diet supplemented with arginine, omega-3 fatty acids and RNA after surgery (B); enteral diet supplemented with arginine, omega-3 fatty acids and RNA before and after surgery (C)</p>	<p>Lymphocyte counts in group C on post-op day 7 were somewhat higher than group a (p=0.07), and significantly higher than group B (p=0.03). Duration of post-op systemic inflammatory response syndrome (SIRS) was significantly shorter in group C than in group A (p&lt;0.05).</p>	<p>“This study reveals that the perioperative immune-enhanced formula may be superior to postoperative control enteral formulas in terms of reducing surgical wound infection and post-operative SIRS.”</p>
<p><i>de Luis DA, et al. Clinical and biochemical outcomes alter a randomized trial with a high dose of enteral arginine formula in postsurgical head and neck cancer Eur J Clin Nutr 2007;61:200-204.</i></p>	<p>To investigate whether postoperative nutrition of head and neck cancer patients, using a higher dose of arginine-enhanced diet (17g/day), could improve nutritional</p>	<p>-Prospective, randomized, controlled clinical trial -72 patients with oral and laryngeal cancer -At surgery, patients were randomly assigned to arginine-enhanced formula or an isocaloric,</p>	<p>Postoperative infection complications were equal in both groups; fistula was less frequent in arginine-enriched group; length of postoperative stay and wound infection was similar in both groups.</p>	<p>“At this dose, arginine-enhanced formula improves fistula rates in postoperative head and neck cancer patients.”</p>

	variables as well as clinical outcomes, when compared with a control enteral diet.	isonitrogenous enteral formula		
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<p><i>Casas-Rodera P et al. Immunoenhanced enteral nutrition formulas in head and neck cancer surgery: a prospective, randomized clinical trial. Nutr Hosp. 2008 Mar-Apr;23(2):105-110.</i></p>	<p>To compare 2 immunoenhanced enteral nutrition formulas effect on postoperative infections, length of stay and inflammatory markers</p>	<p>-Prospective, randomized, controlled clinical trial -44 patients with oral and laryngeal cancer were randomly allocated to one of three groups; arginine-enhanced formula (I); standard polymeric formula (II); arginine-enhanced, RNA and omega-3 fatty acids (III)</p>	<p>Length of postoperative stay was similar between groups; wound infections and general infections were more frequent in the control group; fistula rates were not improved in the enhanced groups; control group saw the highest level of TNF-alpha</p>	<p>“Immunoenhanced nutrition formula improved the infection rate in postoperative head and neck cancer patients”</p>
<p><i>Berk L et al. A randomized, double-blind placebo controlled trial of beta-hydroxy-beta-methylbutyrate, glutamine, and arginine mixture for the treatment of cancer cachexia (RTOG 0122). Support Care Cancer. 2008;16:1179-1188.</i></p>	<p>To investigate if supplementation of specific nutrient known to positively support protein synthesis and reduce protein breakdown will reverse the cachexia process in advanced cancer patients.</p>	<p>-Prospective, randomized, controlled clinical trial -472 patients with stage IV solid tumors -Patients were randomly assigned to receive 3g HMB/14g arginine/14g glutamine or control for 8 weeks -Primary outcome measure was change in lean body mass and skin-fold</p>	<p>Trend towards a higher lean body mass throughout the study for those in the HMB/Arg/Glut group and measured by BIA (p=0.08) and skin-fold measurement (p=0.08)</p>	<p>This trial was unable to adequately test the ability of HMB/Arg/Glut to reverse or prevent LBM wasting among cancer patients.</p>

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