Effects of Curcumin on Tumor Growth and Muscle Mass in a Mouse Model of Cancer Cachexia

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Purpose/Objectives: To determine whether a diet containing 1% curcumin, a highly colored botanical food containing compounds that suppress expression of proinflammatory mediators implicated in the pathobiology of tumor-induced muscle wasting, would preserve muscle mass in two animal models of cancer cachexia.

Design: Four-group experimental design.

Setting: A health sciences animal care unit in the midwestern United States.

Sample: 60 female C57Bl/6 mice.

Methods: Mice were subcutaneously inoculated with Lewis lung carcinoma or B16 melanoma tumor cells. Curcumin was mixed into ground standard rodent food. The animals were fed the standard food or food with 1% curcumin for 17 days. Body weight and food intake were monitored and hind limb muscles, spleen, and tumor mass were weighed on day 17. Data were analyzed using two-way (tumor, diet) analysis of variance.

Main Research Variables: Body weight; plantaris, soleus, and gastrocnemius muscles relative to body weight; spleen; and tumor.

Findings: Food intake was not affected by 1% curcumin in the food. Tumor growth caused significant wasting of skeletal muscles in both animal models. Curcumin did not reduce splenomegaly or preserve body weight or muscle mass in either model, but curcumin did significantly reduced tumor mass in mice with B16 melanoma.

Conclusions: Curcumin may not be beneficial in the treatment of cancer cachexia; however, controlled clinical trials of curcumin in patients with cancer are warranted based on evidence of its antitumor effects in animal models.

Implications for Nursing: Patients frequently self-prescribe complementary and alternative substances after diagnosis and during cancer therapy. Answers to patients' questions about purported effects of these substances must include research findings when possible.

Key Points . . .

- Cancer cachexia causes anorexia, weight loss, and significant wasting of skeletal muscles in patients with advanced or incurable diseases.
- Animal models are useful for exploring the biologic effects of nursing interventions.
- Curcumin, a botanical food with anti-inflammatory effects, slowed growth of melanoma tumors in mice.

Botanical foods contain a large and heterogeneous group of biologically active compounds called phytochemicals. Foods rich in polyphenolic compounds, which include the catechins in green tea, the flavanoids in highly colored fruits and vegetables, and curcuminoids in tumeric, have antioxidant qualities and are thought to be health-promoting (Ferrari, 2004). The compounds also reduce expression or activity of cyclooxygenase-2 (COX-2). COX is the rate-limiting enzyme in metabolism of arachidonic acid; increased expression of the COX-2 isoform of COX is responsible for increased synthesis of eicosanoid mediators of the inflammatory response. Most nonsteroidal anti-inflammatory drugs (NSAIDs) work by inhibiting COX activity. A large body of evidence supports findings that suggest increased expression of COX-2 is associated with tumor growth and that chronic ingestion of NSAIDs reduces the incidence of some cancers (Harris, 2007; Wallace, 2002). Many botanical polyphenolic compounds that suppress COX-2 expression also have been shown to suppress tumor cell growth in vitro and carcinogenesis in laboratory animals (Nishino et al., 2004; Takada, Bhardwaj, Potdar, & Aggarwal, 2004). Several are believed to have chemopreventive potential in humans (Aggarwal & Shishodia, 2006; Surh, 2003; Thomasset et al., 2007).

More than 50% of patients with cancer report using alternative and complementary medicines after diagnosis and during oncology treatment (Vapiwala, Mick, Hampshire, Meta, & Denittis, 2006). Extracts of foods rich in polyphenolic compounds make up a large portion of the self-prescribed complementary and alternative products used to lower the risk of cancer, its recurrence, or to enhance the effectiveness of physician-prescribed antitumor therapies (Adams & Jewell, 2007; HemaIswarya & Doble, 2006); therefore, oncology nurses must ask patients about their use of botanical foods and herbs and answer questions using research data when possible.

Curcumin is a leading polyphenolic agent in clinical studies of botanical compounds for chemoprevention and

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chemotherapy (Hsu & Cheng, 2007; Sharma, Steward, & Gescher, 2007). Curcumin inhibits expression of COX-2 at several points in cell-signaling pathways, including decreased activation of nuclear transcription factor kappa-B (NF-kB), which controls transcription of the COX-2 gene and several proinflammatory cytokine genes, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNFα) (Aggarwal & Shishodia, 2006; Aggarwal, Ichikawa, et al., 2006; Sharma, Gescher, & Steward, 2005; Surh, 2003). Curcumin also blunts the expression of angiogenic growth factors, reducing microvascular blood supply to a growing tumor or its metastases (Aggarwal, Ichikawa, et al.).

Cancer cachexia is a syndrome of anorexia, weight loss, and skeletal muscle wasting seen in patients with advanced or incurable disease. The loss of skeletal muscle mass likely explains much of the fatigue and reduced effort tolerance experienced by patients with cancer cachexia, and interventions to preserve muscle mass in these patients are sorely needed. A growing body of evidence suggests that cancer cachexia is much like a chronic inflammatory condition, associated with increased activation of NF-kB, increased expression of COX-2, elevated serum levels of proinflammatory cytokines such as IL-6 and TNFα, and increased tissue levels of pro-inflammatory eicosanoids (Deans & Wigmore, 2005; DeJong et al., 2005). Although it is unclear how progressive tumor growth might increase the expression or activity of proinflammatory mediators, a growing number of reports indicate that NSAIDs that inhibit COX-2 activity preserve body weight and muscle mass in some animal models of cancer cachexia (Graves, Ramsay, & McCarthy, 2006; McCarthy, Whitney, Hitt, & Al-Majid, 2004), improve functional status (Lai et al., 2008), and prolong survival in terminally ill patients with cancer (Deans & Wigmore; Lundholm, Daneyrd, Korner, Hyltander, & Bosaeus, 2004). Because curcumin reduces expression of COX-2, IL-6, and TNFα (Jeong, Kim, Hu, & Kong, 2004; Surh, 2003), it seems reasonable to test whether curcumin would be beneficial in treatment of cancer cachexia.

Animal models often are useful in examining the biologic mechanisms of symptoms experienced by patients with cancer and for preclinical testing of biologic-based interventions to reduce symptom severity. An animal model of cancer cachexia allows researchers to quantify changes in skeletal muscle mass without concern for subject variations in tumor type, disease stage, activity levels, physicality, or food preferences, all of which can affect skeletal muscle metabolism. In the present study, the researchers elected to examine the effects of a curcumin on tumor growth and muscle mass of mice bearing Lewis lung carcinoma (LLC) or B16 melanoma. Previous laboratory work by the researchers demonstrated that LLC and B16 melanoma tumor cell lines induced a similar degree of skeletal muscle wasting without reducing food intake of the tumor-bearing mice (Graves et al., 2006; McCarthy & Graves, 2006). The LLC cell line constitutively expresses COX-2 and the B16 melanoma cell line does not. Treatment with NSAIDs that specifically or nonspecifically suppress COX-2 activity reduced muscle wasting in mice bearing LLC but not B16 melanoma. Because curcumin inhibits COX-2 expression (Aggarwal & Shishodia, 2006; Aggarwal, Ichikawa, et al., 2006; Surh, 2003), the researchers hypothesized that curcumin would preserve muscle mass in mice bearing LLC, but not B16 melanoma.

Material and Methods

LLC and B16 melanoma tumor cell lines were obtained from American Type Culture Collection (Manassas, VA) and cultured in RPMI 1640 supplemented with 10% fetal calf serum and 1% penicillin and streptomysin (Sigma Chemical Co., St. Louis, MO). Cells were passaged, when confluent, using trypsin (Sigma). Both cell lines are syngeneic for C57Bl/6 mice. Curcumin powder, containing 94% curcumin and 6% other curcuminoids, was obtained from LKT Laboratories (St. Paul, MN). Curcumin powder was mixed into ground rodent food (Harlan Teklad, Indianapolis, IN) to obtain a concentration of 1% (by weight). Animals were allowed free access to ground rodent food in dishes designed to reduce spillage (Unifab Corp., Portage, MI). Preliminary data indicated that mice weighing 20 g ate an average of 3 g of food per day, and the 1% curcumin did not alter food intake compared to animals maintained on ground food without curcumin. A diet containing 1% curcumin approximates a dose of 150 mg/kg of curcumin per day.

Pathogen-free C57Bl/6 female mice weighing 18–20 g were obtained from Harlan Teklad and were acclimated to the housing for three days prior to commencing the experiment. The mice were maintained on a 12-hour light/dark cycle that commenced at 6 am. The mice were housed three to a cage to reduce isolation stress, which meant the researchers could not monitor individual food intake. Therefore, individual mice were weighed twice a week to detect any decrease in body weight that might reflect a decrease in food intake. Experiment 1 examined the effects of curcumin in mice bearing LLC and experiment 2 examined the effects of curcumin in mice bearing B16 melanoma. The research protocol was approved by the Institutional Animal Care and Use Committee.

For each experiment, 18 animals were injected subcutaneously between the scapulae with 5 x 10^5 tumor cells in 0.2 ml phosphate-buffered saline; 12 animals served as healthy controls. A greater number of mice were assigned to the tumor group to allow for exclusion of subjects that did not grow a tumor or showed signs of morbidity (decreased movement, failure to groom, irritation at tumor site) prior to completion of the experiment. On day 1 of tumor growth, the food dishes in three cages housing nine tumor-bearing animals and two cages housing six control animals were replaced with dishes containing 1% curcumin mixed into the ground food. The remaining three cages of nine tumor-bearing and two cages of six control animals were maintained on ground food with no added curcumin. Food dishes were filled and weighed every other day. Previous work had demonstrated that food intake of mice bearing LLC or B16 melanoma tumors declined after day 20 of tumor growth (Graves et al., 2006; McCarthy & Graves, 2006); therefore, all animals were maintained on their respective diet for 17 days.

The animals were euthanized individually on day 17 of tumor growth using inhaled carbon dioxide gas followed by cervical dislocation as specified by the American Veterinary Medicine Association Panel on Euthanasia. Each animal was weighed, and the spleen was quickly removed, weighed, and individually frozen on dry ice. The gastrocnemius, plantaris, and soleus muscles of each hind limb were dissected, individually weighed, and frozen on dry ice. Lastly, the tumor was removed and weighed.

The weight of the right and left muscles was averaged to determine muscle weight. Muscle mass was calculated as muscle weight divided by body weight. Muscle mass and spleen weight were analyzed using two-way (tumor, diet) analysis of variance (ANOVA). Body weights over the course of the experiment were analyzed using repeated measures ANOVA and tumor weight at the time of euthanization was analyzed using Student's t test.

Results

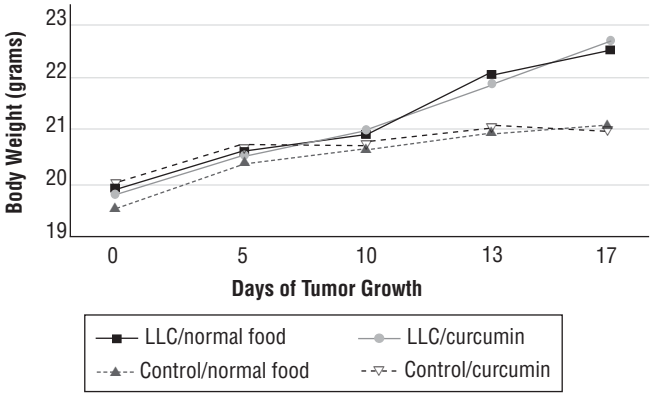
Experiment 1: Lewis Lung Carcinoma

Body weights of the mice on the diet containing 1% curcumin did not differ from mice given the control diet in either the control or tumor-bearing animals. Body weight change over time was greater in the tumor-bearing mice because of the increasing tumor mass ($p < 0.05$) (see Figure 1). However, carcass weight (body weight minus tumor weight) did not differ. Curcumin did not affect growth of the LLC tumor compared to tumor-bearing mice given the control diet (1.0 g versus 1.1 g).

Significant enlargement of the spleen, which would be expected with chronic inflammation, was seen in the tumor-bearing animals ($F [1, 29] = 11.2$, $p = 0.02$). Spleen weight was not reduced in animals fed curcumin in the diet ($p = 0.7$). Weight of the plantaris and the gastrocnemius muscles relative to body weight were reduced significantly in tumor-bearing mice and were not affected by 1% curcumin in the diet (see Table 1). Weight of the soleus muscle was not significantly reduced in the LLC tumor-bearing mice or affected by curcumin.

Experiment 2: B16 Melanoma

Body weight gain of tumor-bearing and control groups of mice was not affected by curcumin, but tended to be greater in tumor-bearing mice, reflecting the contribution of tumor mass to body weight ($p = 0.08$). Carcass weight (body weight minus tumor weight) did not differ. Significant enlargement of the spleen was seen in the tumor-bearing animals ($F [1, 29] = 13$, $p = 0.001$) and was not reduced in animals given curcumin in their diet ($p = 0.7$) (see Figure 2). The relative weight of the gastrocnemius, plantaris, and soleus muscles were significantly less in B16 melanoma tumor-bearing mice, and muscle weight was not affected by curcumin (see Table 2). However, weight of the B16 melanoma tumor was less in mice fed 1% curcumin compared to mice fed the control diet (0.8 g versus 1.5 g, $p = 0.003$).



Note. Data were analyzed using repeated measures analysis of variance. Body weight of tumor-bearing animals (square and circle symbols) was significantly different from controls (triangle symbols) ($p < 0.05$).

Figure 1. Mean Body Weight Over Time of Mice in Experiment 1

Table 1. Hind Limb Muscle Mass in Grams in Experiment 1

	Gastrocnemius[a]		Plantaris[a]		Soleus	
Group	Weight	SD	Weight	SD	Weight	SD
Control (n = 6)	0.46	0.02	0.06	0.002	0.03	0.002
Control and curcumin (n = 6)	0.46	0.02	0.06	0.005	0.03	0.001
Lewis lung carcinoma (n = 9)	0.41	0.03	0.05	0.009	0.03	0.005
Lewis lung carcinoma and curcumin (n = 9)	0.42	0.04	0.05	0.006	0.03	0.003

[a] Significant effect of tumor, $p < 0.01$

Note. Data were analyzed using two-factor (tumor, diet) analysis of variance.

Discussion

Skeletal muscle wasting plays a major role in the morbidity and mortality of cancer cachexia. Proinflammatory cytokines and prostanoids play a role in cancer cachexia, and NSAIDs that inhibit COX activity have been shown to preserve muscle mass in tumor-bearing mice (Graves et al., 2006; McCarthy et al., 2004) and prolong survival in patients with cancer cachexia (Deans & Wigmore, 2005; Lundholm et al., 2004). Curcumin, a botanical polyphenol compound in the spice turmeric, has been shown to suppress expression of several proinflammatory mediators of tumor-induced muscle wasting, including IL-6, TNFα, and COX-2. LLC and B16 melanoma are tumor cell lines that induce skeletal muscle wasting in tumor-bearing mice. LLC tumor cell line expresses COX-2 and B16 melanoma does not; therefore, the researchers hypothesized that ingestion of 1% (150 mg/kg per day) curcumin in the diet would preserve muscle mass in mice bearing LLC but not in those bearing B16 melanoma.

In the current study, the researchers observed that growth of LLC or B16 melanoma tumors were associated with wasting of the gastrocnemius and plantaris muscles and enlargement of the spleen, indicative of a chronic inflammatory response in the tumor-bearing mice. Curcumin had no effect on muscle mass or spleen size in the tumor-bearing mice consuming 1% (150 mg/kg per day) curcumin in the diet. The dose of curcumin used in the current study may have been too low to achieve a sufficient anti-inflammatory effect. However, similar findings were reported in mice bearing murine adenocarcinoma tumors that consumed 150–300 mg/kg curcumin per day in their diet (Wyke, Russell, & Tisdale, 2004). Some researchers questioned whether gastrointestinal absorption of curcumin was sufficient enough to reach bioactive or

therapeutic serum levels of curcumin. However, intraperitoneal injection of 20 mcg/kg curcumin did not reverse muscle wasting in rats bearing Yoshida hepatoma (Busquets et al., 2001), although it did reduce muscle loss in healthy animals injected with lipopolysaccharide, a potent inducer of COX-2 and TNFα expression (Jin & Li, 2007). Other studies demonstrated that a diet supplemented with 1% curcumin suppressed activation of NF-kB in healthy animals but did not suppress activation of NF-kB or preserve muscle mass in an animal model of disuse muscle atrophy or muscular dystrophy (Durham, Arbogast, Gerkin, Li, & Reid, 2006; Farid, Reid, Li, Gerken, & Durham, 2005). Taken together, the data suggest that curcumin is not likely to reduce skeletal muscle wasting in patients with cancer cachexia. The data also suggest that tumor-induced skeletal muscle wasting may involve intracellular signaling pathways or molecules not affected by curcumin.

In Experiment 2 of the current study, the researchers observed that 1% curcumin in the diet (150 mg/kg per day) reduced tumor growth in mice bearing B16 melanoma. A similar antitumor effect of 500 mg/kg curcumin given orally, or 20 mcg/kg injected intraperitoneally, was observed in immune-deficient mice bearing human ovarian tumors and in rats bearing Yoshida hepatoma (Busquets et al., 2001; Lin et al., 2007). Reports that a diet supplemented with 2% curcumin reduced metastasis of human breast or prostate tumors in immune deficient mice also exist (Aggarwal et al., 2005; Hong, Ahn, Bae, Jeon, & Choi, 2006). Other research even suggests that 0.5% curcumin in the diet (75 mg/kg per day) may reduce adenoma formation in a strain of mice genetically predisposed to develop colon tumors (Perkins et al., 2002). Taken together, the data from animal models of cancer suggest that curcumin may be effective in slowing primary or metastatic growth of some tumors.

In the current study, the same dose of curcumin that inhibited growth of B16 melanoma did not affect growth of LLC. Others have shown in vitro that curcumin had potent antiproliferative and proapototic effects in three human melanoma cell lines (Siwak, Shishodia, Aggarwal, & Kurzrock, 2005). The current study demonstrates that the anti-proliferative effect of curcumin may slow melanoma tumor growth in vivo. The lack of effect in mice bearing the LLC tumor line suggests that tumor cell lines may differ in the expression or activity of growth factors affected by curcumin. Further study is needed to determine which tumor types or signaling molecules involved in tumor cell growth may or may not be susceptible to the antitumor effects of curcumin (Aggarwal, Sethi et al., 2006; Aggarwal, Ichikawa et al., 2006).

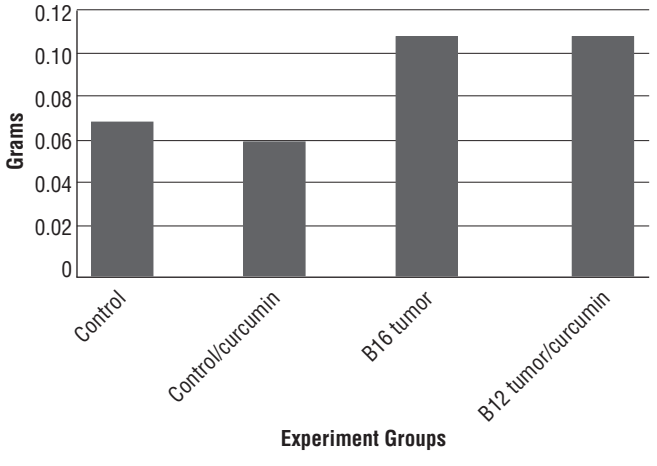
In summary, the hypothesized effect of curcumin on skeletal muscle mass of mice bearing LLC was not supported in the current study. The results of the current and other preclinical studies using animal models of tumor-induced skeletal muscle wasting suggest that curcumin may not be helpful in slowing the loss of skeletal muscle mass in patients with cancer cachexia. However, controlled clinical trials of curcumin in patients with cancer are warranted based on evidence of the antitumor effects of curcumin obtained from animal models of carcinogenesis and tumor growth (Sharma et al., 2007). Although no evidence suggests that curcumin can prevent cancer or slow tumor growth in humans, data from phase 1 clinical trials shows that curcumin is well tolerated at doses up to 8 g daily up to four months (Hsu & Cheng, 2007). However, data also show that patients diagnosed with cancer often self-administer complementary and alternative medicinal compounds to reduce the effects of cancer or cancer therapies (Vapiwala et al., 2006). No evidence suggests that curcumin might be harmful or negatively affect medically directed cancer therapies (Garg, Buchholz, & Aggarwal, 2005; HemaIswarya & Doble, 2006). Some evidence exists from immune-deficient mice inoculated with human ovarian, breast, or pancreatic cancer cells that curcumin may enhance the antitumor effects of docetaxel, paclitaxel, and gemcitabine (Aggarwal et al., 2005; Kunnamakkara et al., 2007; Lin et al., 2007). More clinical studies of the effects of curcumin and other botanical polyphenolic compounds are needed before healthcare professionals can fully understand the potential benefits to chemoprevention and cancer treatment.

Table 2. Hind Limb Muscle Mass in Grams in Experiment 2

	Gastrocnemius[a]		Plantaris[a]		Soleus	
Group	Weight	SD	Weight	SD	Weight	SD
Control (n = 6)	0.45	0.02	0.06	0.003	0.032	0.003
Control and curcumin (n = 6)	0.45	0.02	0.06	0.002	0.031	0.002
B16 melanoma (n = 9)	0.41	0.03	0.05	0.006	0.029	0.002
B16 melanoma and curcumin (n = 9)	0.42	0.03	0.05	0.007	0.029	0.002

[a] Significant effect of tumor, $p < 0.02$

Note. Data were analyzed using two-factor (tumor, diet) analysis of variance.



Note. Data were analyzed using two-way analysis of variance. The control groups and tumor groups were significantly different ($p < 0.05$).

Figure 2. Mean Spleen Weight of Mice in Experiment 2

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