

## Healthy Adults

### *Human Immunology.*

Yin Z, Fujii H, Walshe T. Effects of active hexose correlated compound (AHCC) on the frequency of CD4+ and CD8+ T cells producing IFN- $\gamma$  and/or TNF- $\alpha$  in healthy adults. 2010 Dec; 71(12): 1187-90.

**Topic:** Does AHCC have an effect on immune function of healthy adults aged 50 or greater?

**Background:** AHCC has been shown to have an enhancing effect on immune function of humans and rodents, including an increase of natural killer (NK) cell activity, interleukin-12 production and resistance to bacterial infection. Animal studies have shown that the effects of AHCC are more evident in hosts with impaired immune function, which is measured as its ability to enhance immune function parameters specifically in a murine tumor model, such as interferon (IFN)- $\gamma$  production by CD8 +T cells and the numbers of NK and  $\gamma\delta$ T cells. However, it is largely unknown whether AHCC could enhance immune parameters such as (IFN)- $\gamma$  and tumor necrosis factor (TNF- $\alpha$ ) production by CD4+ and CD8 + T cells in humans, in particular, elderly adults with increased risk of infection and malignancy.

**Study type:** Human clinical intervention trial.

**Study design:** Open-label trial: Subjects were treated with AHCC for 60 days. Peripheral blood was collected at base line, 30 and 60 days during supplementation and another 30 days after supplementation was discontinued. The production of interferon IFN- $\gamma$  and TNF- $\alpha$  by CD4+ and CD8 + T cells was measured by flow cytometry.

**Subjects:** 30 healthy adults over the age of 50.

**Dosage:** 3 grams of AHCC per day (3-500 mg capsules twice daily).

**Results:** AHCC supplementation resulted in the following significant changes compared with base line:

- The frequency of CD4+ and CD8 + T cells producing IFN- $\gamma$  alone, TNF- $\alpha$  alone or both increased during AHCC intake
- The frequency of such cells remained high even 30 days after discontinuing AHCC

**Conclusion:** "Our results suggest that AHCC can enhance CD4+ and CD8 + T cell immune responses in healthy persons via increasing production of cytokines IFN- $\gamma$  and TNF- $\alpha$  from T cells. Effects were seen after 30 days, and remained up to 30 days after discontinuing the compound. AHCC may improve immune response against pathogens through this mechanism."

### *Nutrition and Cancer.*

Terakawa N, Matsui Y, Satoi S, Yanagimoto H, Takahashi K, Yamamoto T, Yamao J, Takai S, Kwon AH, Kamiyama Y. Immunological effect of active hexose correlated compound (AHCC) in healthy volunteers: a double-blind, placebo-controlled trial. 2008; 60(5): 643-51.

**Topic:** Does AHCC have an effect on immune responses in healthy volunteers?

**Background:** Biological response modifiers (BRMs) are substances that stimulate the body's response to infection and disease. Attempts have been made to treat cancer with BRMs, but their clinical efficacy has not been clearly confirmed. AHCC has had numerous positive clinical results on cancer patients without any adverse effects, but has not been investigated for its effect on immune response in humans. The immune response can be measured by dendritic cells (DCs), the most potent antigen-presenting cells capable of priming tumor-specific T cells. DCs use in cancer immunotherapy appears to be a promising way to elicit and expand efficient antitumor immune responses.

**Study type:** Human clinical intervention trial.

**Study design:** Double-blind randomized placebo controlled: Subjects were treated with AHCC daily for 4 weeks. Blood samples were taken at base line and again after 4 weeks. The number of circulating DC1 and DC2 cells, natural killer (NK) cells and CD4+/CD8+ T lymphocytes was measured by flow cytometry. In addition, other immune function parameters were measured.

**Subjects:** 21 healthy volunteers.

**Dosage:** 3 grams of AHCC per day (n=10) or placebo (n=11).

**Results:** Volunteers supplemented with AHCC had the following significant changes:

- Greater number of total DCs than at base line and compared with control
- The number of DC1 cells was greater after AHCC intake than at base line and the AHCC group had a tendency to have higher DC1s than control
- DC2s were significantly increased after 4 weeks compared with control
- The allo-stimulatory activity of DC1s was also increased after intake compared with control as measured by the mixed lymphocyte reaction (MLR)

**Conclusion:** "These results suggest that AHCC could be an effective modulator of immunological function in patients with cancer. AHCC acts as a promising BRM."

## Healthy Adults

*Presented at Experimental Biology Meeting. April 2010.*

Gardner E, Beli E, Kempf L, Fujii H. Active hexose correlated compound (AHCC) improves immune cell populations after influenza vaccination of healthy subjects.

**Topic:** Does AHCC have an effect on immune response of healthy adults after influenza vaccinations?

**Background:** AHCC has been shown to have an enhancing effect on immune function of humans and rodents, including an increase of natural killer (NK) cell activity, interleukin-12 production and resistance to bacterial infection.

**Study type:** Human clinical intervention trial.

**Study design:** Randomized, double-blind placebo-controlled trial: Subjects were treated with AHCC or a placebo on the day of vaccination and for 3 weeks following vaccination. Blood was drawn at immunization and 2 weeks later for phenotypic analysis of lymphocytes using flow cytometry.

**Subjects:** 29 healthy adults.

**Dosage:** 3 grams of AHCC per day (n=14), placebo (n=15).

**Results:** AHCC supplementation resulted in the following changes compared with control:

- The fold increases in percentages of T cells, CD8+ T (cytotoxic) cells and CD56+ (NK) cells (but not CD4/CD8 ratios) were significantly higher than at vaccination for AHCC-supplemented subjects
- CD56 bright cytotoxic NK cells were higher in AHCC group
- AHCC supplementation had a more dramatic effect on immune cell phenotypes after vaccination of subjects over 60 years old

**Conclusion:** "This study suggests that short-term AHCC supplementation may be a good therapeutic intervention to sustain, or increase, the immune response to influenza vaccination in healthy subjects."

*Journal of Nutritional Science and Vitaminology.*

Spierings E, Fujii H, Sun B, Walshe T. A Phase I study of the safety of the nutritional supplement active hexose correlated compound, AHCC, in healthy volunteers. 2007 Dec; 53(6): 536-9.

**Topic:** Is AHCC safe and tolerable in healthy subjects?

**Background:** AHCC has been used for many years as a dietary supplement to enhance the immune system and in clinical trials as adjunctive treatment in hepatocellular cancer. Its safety has been previously based on anecdotal reports and its use in clinical practice. Phase 1 clinical trials are used to make the initial safety assessment of compounds with potential medical uses.

**Study type:** Human clinical intervention trial.

**Study design:** Phase I clinical trial: Subjects were treated with AHCC daily for 14 days. Laboratory data was obtained at base line and after 14 days of exposure to AHCC, and adverse events were monitored by a nondirected review of systems questionnaire 3 times during the trial.

**Subjects:** 26 healthy male or female subjects between 18 and 61 years of age.

**Dosage:** 9 grams of AHCC per day (liquid form).

**Results:** Laboratory results and adverse events were reported as follows:

- Two subjects (7%) dropped out because of nausea and intolerance of the liquid
- Nausea, diarrhea, bloating, headache, fatigue and foot cramps occurred in a total of 6 subjects (20%) but were mild and transient
- There were no laboratory abnormalities

**Conclusion:** "The adverse effects of 9 grams of liquid AHCC per day, a higher dose than used in routine clinical applications, are minimal and the dose was tolerated by 85% of the subjects. This trial supports the anecdotal evidence that AHCC is a safe supplement in clinical practice and that the side effects are generally mild and tolerable."

## Prostate Cancer

*Japanese Journal of Clinical Oncology.*

Sumiyoshi Y, Hashine K, Kakehi Y, Yoshimura K, Satou T, Kuruma H, Namiki S, Shinohara N. Dietary administration of mushroom mycelium extracts in patients with early stage prostate cancers managed expectantly: a phase II study. 2010 Oct; 40(10): 967-72.

**Topic:** Does AHCC have an effect on patients with early stage prostate cancer?

**Background:** There has been a marked increase in the incidence of prostate cancer, and owing to widespread use of PSA screening, most prostate cancers are discovered at an extremely early stage. An alternative to active treatment, expectant management (also known as “watchful waiting”) has been adopted as a treatment for prostate cancer. This has resulted in interest of prostate patients in using complementary and alternative medicine, such as dietary supplements. Few clinical trials on dietary supplements on early stage prostate cancer have been conducted. AHCC has been reported to have immune-stimulating activity, anticancer activity and cancer-preventative actions, and therefore its effect on early stage prostate cancer is being investigated.

**Study type:** Human clinical intervention trial.

**Study design:** Open-label trial: Patients were treated with AHCC for 6 consecutive months, and for willing patients, the period was extended for an additional 6 months. A PSA test and biochemical examination were performed every 2 months. In addition, immune parameters such as T helper 1/T helper 2 ratio and NK cell activity were monitored. A questionnaire survey of the state-trait anxiety inventory (STAI) – a test for measuring anxiety – was given before treatment and after 6 months.

**Subjects:** 74 total: 40 prostate patients undergoing expectant management and 34 patients who had already undergone expectant management for 6 months or more.

**Dosage:** 4.5 grams of AHCC per day.

**Results:** AHCC supplementation resulted in the following changes:

- Changes in PSA before and after treatment were substantially stable
- In patients for which expectant management had been continued for 6 months or more before the trial, a prolonged PSA doubling time (PSADT) was seen with AHCC administration
  - Prior to AHCC, 12/31 (39%) of patients had PSADT of 120 months or more, and after 6 months of AHCC administration, 17/31 (55%) had PSADT of 120 months or more

### Results

(cont'd):

- To the lower end, 12/31 (39%) of patients showed a PSADT less than 24 months, and following 6 months of AHCC, this fell to 9/31 (29%)
- Anxiety significantly decreased after 6 months of treatment in patients exhibiting strong anxiety before the start of the trial

**Conclusion:** “These results suggest that dietary uptake of AHCC contributes to the stabilization of the disease status in patients with early stage prostate cancer who are expectantly managed.”

## Prostate Cancer

### *International Journal of Immunotherapy.*

Ghoneum M, Wimbley M, Salem F, McKlaine A, Attalah N, Gill G. Immunomodulatory and anti-cancer effects of active AHCC. 1995; X1(1): 23-28.

**Topic:** Does AHCC have immunomodulatory and anti-cancer effects in cancer patients?

**Background:** The increased incidence of spontaneous tumors in immune-suppressed individuals, as well as those with congenital or acquired immunodeficiencies, indicates that the immune system can provide a major mechanism for host resistance against cancer and infectious diseases. Several biological response modifiers (BRMs) have been developed to stimulate the immune system for tumor fighting, but their use is limited because of their severe side effects. AHCC possesses BMR activity, but without side effects and is therefore investigated in cancer patients.

**Study type:** Human clinical intervention trial.

**Study design:** Open-label trial: Subjects were treated with AHCC for up to 17 months. Tumor-associated antigens (TAAs) for each type of malignancy was measured prior to AHCC treatment and at 3- to 40-week intervals. Natural killer (NK) cell activity was also monitored.

**Subjects:** 11 cancer patients with advanced malignancies.

**Dosage:** 3 grams of AHCC per day.

**Results:** Supplementation with AHCC had the following results:

- A significant decline in TAA occurred in 8 out of the 11 patients with different types of malignancies
- PSA levels in prostate cancer patients and CA 125 levels in ovarian cancer patients decreased as early as 1 to 2 months and reached normal levels within 1 to 4 months
- 9 out of 11 patients demonstrated marked increase in NK activity as early as 2 weeks after treatment
- The percentages of patients with complete remission were as follows: (i) prostatic (66%); (ii) ovarian (66%). (iii) multiple myeloma (50%); (iv) breast, 33% complete remission and 2 partial
- *In vitro* studies showed that AHCC possesses suppressive effects on tumor cell growth

**Conclusion:** "The high augmentory effect of AHCC and the absence of notable side effects make AHCC a promising immunotherapeutic agent for the treatment of cancer patients."

### *Anti-Cancer Drugs.*

Turner J, Chaudhary U. Dramatic prostate-specific antigen response with active hexose correlated compound in metastatic castration-resistant prostate cancer. 2009 Mar; 20(3): 215-216.

**Topic:** Does AHCC have an effect on castration-resistant prostate cancer (CRPC)?

**Background:** The median survival of patients with castration-resistant prostate cancer (CRPC) is approximately 18 months. CRPC is defined as progression of disease with serum testosterone controlled below a castrate level. After failure of hormonal therapy, secondary hormonal maneuvers, remain the mainstay of treatment. The use of unconventional herbal supplements in many malignancies has been increasing over the last several years. It has been demonstrated that AHCC has activity in prostate cancer, ovarian cancer and multiple myelomam and therefore it is hypothesized that AHCC may have potential activity against CRPC.

**Study type:** Human clinical intervention trial.

**Study design:** Case study. A Caucasian male with CRPC with high-risk features who benefited less than 6 months from initial complete androgen blockade began self-administration of AHCC.

**Subjects:** 1 Caucasian male (66 years old) with CRPC.

**Dosage:** Not reported.

**Results:** The self-administration of AHCC resulted in a dramatic PSA decrease within 1 month, which continued to control his disease for over 6 months from initial supplementation with AHCC.

**Conclusion:** "Based on limited studies to date, it seems that AHCC may have a role in the management of prostate cancer patients, especially those who have failed hormonal therapy. Larger studies are required to analyze the impact on this new therapy in prostate cancer patients."

## Liver Cancer

### *Journal of Hepatology.*

Matsui Y, Uhara J, Sato S, Kaibori M, Yamada H, Kitade H, Imamura A, Takai S, Kawaguchi Y, Kwon AH, Kamiyama Y. Improved prognosis of postoperative hepatocellular carcinoma patients when treated with functional foods: a prospective cohort study. 2002 Jul; 37(1): 78-86.

**Topic:** Can AHCC improve the prognosis of hepatocellular carcinoma (HCC) patients following surgical treatment?

**Background:** The incidence of hepatocellular carcinoma (HCC) is distributed widely over different geographical areas. The prevention and treatment of the recurrence of HCC following hepatic resection has been studied extensively. However, the prognosis for HCC remains unsatisfactory, with the 5-year survival rate after primary surgical treatment at approximately 40% in Japan. In addition to the treatments mentioned above, there have been many attempts to treat the cancer by stimulating with biological response modifiers (BRMs), but the clinical efficacy of these substances has not been clearly confirmed. AHCC may be considered a potent BRM in the treatment of cancer patients, and therefore the effect on HCC is being investigated.

**Study type:** Observational study.

**Study design:** Prospective cohort study: From February 1, 1992 to December 31, 2001, a total of 269 consecutive patients with histologically confirmed HCC were studied. All of the patients underwent resection of a liver tumor. The enrolled patients were addressed to each arm of the study based on their choice of the therapeutic options, and were trusted with the self-administration of AHCC. Time to treatment failure (disease recurrence or death) and 10 parameters related to liver function after surgery were examined.

**Subjects:** 269 consecutive patients with histologically confirmed HCC.

**Dosage:** 3 grams of AHCC per day (n=113).

**Results:** The AHCC group had the following significant differences compared with control group:

- Longer non-recurrence period
- Increased overall survival rate

**Conclusion:** "This study suggests that AHCC intake can improve the prognosis of postoperative HCC patients."

### *Asian Pacific Journal of Allergy and Immunology.*

Cowawintaweewat S, Manoromana S, Sriplung H, Khuhaprema T, Tongtawe P, Tapchaisri P, Chaicumpa W. Prognostic improvement of patients with advanced liver cancer after active hexose correlated compound (AHCC) treatment. 2006 Mar; 24(1): 33-45.

**Topic:** Does AHCC have an effect on patients with advanced liver cancer?

**Background:** Liver cancer is the sixth most common cancer worldwide, with widely varying incidences over different geographical areas. It is the third most common cause of cancer mortality. Most patients with liver cancer are diagnosed at a late or advanced state. Many attempts have been made to treat this cancer, including approaches aimed at stimulating the patient's immune response using biological response modifiers (BRMs). AHCC, a promising BRM, has been found to improve the prognosis of hepatocellular carcinoma patients following surgical treatment and is therefore being investigated to assess whether it could prolong survival and improve prognosis of patients with advanced liver cancer.

**Study type:** Human clinical intervention trial.

**Study design:** Randomized prospective, placebo-controlled trial: Patients were randomized to receive supplementation with AHCC or a placebo until the end of their lives. Clinical parameters were monitored monthly, including quality of life, hematological parameters, biochemical parameters in serum and immunological parameters in citrated plasma. MRIs were also performed for patients who survived for more than 1 year.

**Subjects:** 44 patients with advanced liver cancer.

**Dosage:** 6 grams of AHCC per day (n=34), placebo (n=10).

**Results:** The following results were reported for patients supplemented with AHCC when compared with control group:

- A significantly prolonged survival
- Quality of life in terms of mental stability, general physical health status and the ability to have normal activities were significantly improved after 3 months of supplementation
- Serum level of albumin and percentage of lymphocytes in blood, were significantly higher
- Slightly increased levels of total IL-12 and neopterin



## Liver Cancer (cont'd)

### Results (cont'd):

- In the patient who survived more than 24 months, all 6 parameters seemed not to change vitally, showing a good prognosis that correlated with the survival. In addition, the spider nevi (an abnormal collection of blood vessels near the surface of the skin commonly found in liver cancer patients) on this patient's chest disappeared after 3 months of treatment with no new occurrence until 2 years of follow-up. MRI pictures of his liver mass using magnetic resonance imaging from 2002 (the start of treatment) to 2005 showed that there was no change in tumor size and no new lesion appeared.

**Conclusion:** "This study suggests that AHCC intake could prolong the survival and improve the prognosis of patients with advanced liver cancer and delay the gradual decline of their physiological status."

## Breast and Lung Cancer

*Presented at the 16th AHCC Research Association, November 2008.*  
Ishizuka, R. Extension of survival terms with improved QOL on stage IV cancer of the lung and breast: from the long-term follow-up for 11 years under individual EBM with AHCC and GCP.

**Topic:** Does AHCC in combination with GCP extend survival and quality of life in stage IV lung and breast cancer patients?

**Background:** According to the domestic statistics on cancer death in 2006, 63,255, lung cancer has been increasing and has the worst cancer mortality in Japan. Breast cancer has moved to the fourth. AHCC and GCP (genistein combined polysaccharide, a novel functional health food produced by the fermentation of soybean isoflavone extracts with basidiomycetes mushrooms) have been used in individual evidence-based medicine for stage IV lung and breast cancer. This report does a long-term follow-up on these cases.

**Study type:**

**Study design:** Observational study.

Retrospective cohort study: The subjects were breast and lung cancer patients who were treated with AHCC and GCP. Lung cancer patients had already undergone evidence-based chemotherapy; however, most of them discontinued or refused owing to its non-effect or side effects. Immunotherapy administering AHCC daily to the patients for nearly 2 weeks, co-administration with GCP, was conducted when they restored appetite and mental well-being. The results were compared with the prognosis of breast cancer described in the investigation report of national breast cancer patient registration as a reference data.

**Subjects:** 35 patients with stage IB-IV lung cancer.  
32 patients with stage IV breast cancer.

**Dosage:** 2.25–4.5 grams of AHCC and 0.96–1.92 grams of GCP.

**Results:** Compared against the survival rates in American Society of Clinical Oncology (ASCO) reference data, this retrospective study reported the following observations:

- 1-year, 2 year and 3-year survival rates for stage IV lung cancer increased to 77.1%, 54.3% and 31.4%, respectively
- Improvement of 1-year to 3-year survival rates and prolongation of median survival time (MST) for lung cancer stage IV
- QOL scores of 35 cases were rated A to C by 77.2% of patients, which contributed to reducing final hospitalization time

## Breast and Lung Cancer

### Results

#### (cont'd):

- Survival terms for breast cancer patients for 3 years, 4 years and 5 years were 65.6%, 43.8% and 28.1%, respectively
- Mean survival terms for breast cancer patients were 5 years, 2 months after recurrence and 7 years, 11 months after initial diagnosis
- Extension of survival terms was confirmed
- QOL scores on living cases reported a score of A or B (100%), and scores for those who did not survive were A-B (50%) and C (50%)

**Conclusion:** “AHCC and GCP could contribute to the extension of survival terms and improved QOL on cancer therapy, which seems to step toward a clinical evidence-based medicine.”

### *International Journal of Integrative Oncology.*

Matsui, Y, Kamiyama, Y. Retrospective study in breast cancer patients supplemented with AHCC. 2009; Vol. 3 No. 2.

**Topic:** Does AHCC have an effect on patients with advanced breast cancer?

**Background:** Breast cancer ranks third after gastric and lung cancers in the cause of cancer death of Japanese women. Breast cancer can be detected early by self-examination, and a complete cure is also expectable if it is excised at an early stage. However, it is a fact that advanced recurrent breast cancer is most often incurable and is mainly subjected to a supportive therapy and treatment for quality-of-life improvement. Immunotherapy, in the form of AHCC, may affect the prognosis of advanced breast cancer patients.

**Study type:** Retrospective cohort study.

**Study design:** The study period was 6 years from May 1996 to 2002, and the subjects were breast cancer patients who were treated with AHCC. The subjects received operative treatment of breast cancer during a 13-year period from October 1987 to September 2000. The commencement of AHCC supplementation was differed since AHCC was administered to the patients in accordance with their requests, with most patients commencing AHCC intake due to reappearance. The results were compared with the prognosis of breast cancer described in the investigation report of national breast cancer patient registration as reference data.

**Subjects:** 47 patients with various stages of breast cancer.

**Dosage:** Not reported.

**Results:** Using the national breast cancer patient registration as reference data, this retrospective study reported the improved prognosis of stage IV patients relative to the national average. Since the stage I-III patients at the center all had recurring cancer while the national average includes both recurring and non-recurring cancers, a meaningful comparison could not be made and the results were not statistically significant.

**Conclusion:** “The retrospective study in breast cancer patients with AHCC suggested that AHCC might contribute to improving the prognosis in stage IV, although the improvement remains to be elucidated in stages I, II and III. Therefore, it is considered that a randomized controlled trial of AHCC in breast cancer patients is worthy enough to perform in the future.”

## Gastric and Colon Cancer

### *Natural Medicine Journal.*

Kawaguchi, Y. Improved survival of patients with gastric cancer or colon cancer when treated with active hexose correlated compound (AHCC): effect of AHCC on digestive system cancer. 2009 September; 1(1): 1-6.

**Topic:** Does AHCC have an effect on the survival rate of patients with gastric cancer or colon cancer?

**Background:** Gastric cancer is the second most common cause of cancer death, and colorectal cancer is the third most commonly diagnosed cancer worldwide. Current treatment options for colon cancer and gastric cancer include surgical resection and/or chemotherapy regimes. However, both forms of cancer have poor survival rates. The 5-year survival for patients with unresectable metastatic colon cancer is less than 10% and gastric cancer has an estimated age-adjusted survival rate of 33-44% in the United States and 51-54% in Japan. Tumor immunotherapy, specifically the use of biological response modifiers (BRMs), may provide another therapeutic option in an integrated approach to gastric cancer and colon cancer treatment. AHCC has demonstrated immune stimulating activity and may be a potent BRM in cancer therapy. Therefore, its effect on the survival rate of patients with gastric cancer or colon cancer is investigated.

**Study type:** Observational study.

**Study design:** Prospective cohort study: Patients with a histopathological diagnosis of gastric or colon cancer were recruited to receive oral AHCC as a postoperative adjunctive therapy in conjunction with standard chemotherapy. The cumulative survival rates for gastric and colon cancer patients were analyzed by Kaplan-Meier method.

**Subjects:** 132 patients diagnosed with gastric cancer, 113 patients diagnosed with colon cancer.

**Dosage:** For stage I, II or III patients: 3 grams of AHCC per day (1 g three times per day). For stage IV patients: 6 grams of AHCC per day (2 g three times per day).

**Results:** AHCC supplementation resulted in the following difference in survival rate:

- Improved cumulative 5-year survival rates for patients with gastric cancer (stage IA to stage IIIA) compared with other Japanese institutions

### **Results**

**(cont'd):** • Improved cumulative 5-year survival rates for patients with colon cancer (stage II to stage IIIA) compared with other Japanese institutions

**Conclusion:** "AHCC is a potent BRM that may improve survival in patients with early stage gastric or colon cancer and warrants further investigation as an adjunctive immunotherapeutic in gastric and colon cancer treatment."

## Pancreatic and Biliary Cancer

Presented at the 40th APA (American Pancreatic Association), November, 2009.

Yanagimoto H, Satoi S, Toyokawa H, Yamamoto T, Hirooka S, Yamao J, Araki H, Matsui Y, Kwon A. The beneficial effect of active hexose correlated compound (AHCC), a health food component, in patients with pancreatic or biliary tract cancer who underwent chemotherapy.

**Topic:** Does AHCC have an effect on patients with pancreatic or biliary tract cancer who underwent chemotherapy?

**Background:** AHCC has been previously shown to enhance immune function in healthy volunteers and with the improved prognosis in hepatocellular carcinoma patients. Cancer chemotherapy is effective in many cases; however, there is still a concern to control its side effects. The effect of AHCC on chemotherapy has not been assessed. Therefore, this study investigates whether AHCC alleviates the side effects caused by chemotherapy in the patients with pancreatic or biliary tract cancer.

**Study type:** Human clinical intervention trial.

**Study design:** Open-label, non-randomized phase II study: Postoperative patients with histologically or cytologically proven adenocarcinoma of pancreas or biliary tract, who underwent chemotherapy with gemcitabine, were studied. Gemcitabine was given intravenously at a dose of 1,000 mg/mL once a week for three weeks, followed by 1 week of rest. Patients were divided into two groups that were given AHCC (n=37) or nothing (n=38). The assessment of hematological and non-hematological toxicity was performed over 2 months during the chemotherapy.

**Subjects:** 73 patients with PS of 0-1, and adequate organ function.

**Dosage:** Not reported.

**Results:** AHCC supplementation resulted in the following changes compared with the control group:

- The hemoglobin (Hb) level after chemotherapy in AHCC group was significantly higher
- The taste alteration after chemotherapy in AHCC group was significantly lower

**Conclusion:** "It is suggested that AHCC could alleviate side effects of chemotherapy and that the nutritional state during chemotherapy might be maintained by improving the taste alteration. Further clinical trials will be necessary to clarify the beneficial effect of AHCC."

## Head and Neck Cancer

*International Journal of Clinical Medicine, 2, 588-592 (2011).*

Parida D, Wakame K, Nomura T. Integrating complimentary and alternative medicine in the form of active hexose correlated compound (AHCC) in the management of head & neck cancer patients.

**Topic:** Can AHCC be used in the treatment of head and neck cancer patients?

**Background:** In the state of Meghalay, India, the incidence of cancer of the head and neck region is highest in males, while esophageal cancer is highest in females. This is directly correlated to the high use of tobacco.

**Study type:** Human clinical intervention trial.

**Study design:** Open-label trial: Patients were administered AHCC every morning 3 days prior to chemotherapy and followed up to 1 week post chemotherapy.

**Subjects:** 25 patients of advance state (T3-T4) head and neck cancer.

**Dosage:** 3 grams of AHCC per day.

**Results:** AHCC supplementation resulted in the following observations:

- All patients tolerated AHCC with no added symptoms
- 20 patients reported feeling better and stronger than before at the time of initiation of chemotherapy cycles
- Almost all patients reported better appetites after they started to take AHCC
- In 12 patients who required blood transfusions before chemotherapy cycles, a decrease in the rate of fall of hemoglobin was observed and only 3 patients subsequently required blood transfusions prior to chemotherapy
- 22 patients has a reduction of chemotherapy side effects like nausea, vomiting, loose motion/constipation, etc.
- Tumors regressed in 11 patients
- 8 patients stabilized

**Conclusion:** "It can be concluded that AHCC is safe to administer and definitely helps cancer patients in reducing side effects of chemotherapy, improving sense of well-being and preparing them mentally and physically to continue and tolerate further chemotherapy cycles."

## Reduction of Chemotherapy Side-Effects

*Presented at the 17th AHCC Research Association, 2009.*

Sakaue M, Maeda K, Igura T, Kitagawa T, Sumi R, Hirai K, Kondo K, Ito T. Phase I/II clinical study of AHCC as adverse effect reducer in cancer patients with chemotherapy (the 3rd report).

**Topic:** Is AHCC safe and can AHCC reduce the chemotherapy-induced adverse effects in cancer patients?

**Background:** Cancer chemotherapy is effective in many cases; however, there is still a concern to control its side effects. The effect of AHCC on chemotherapy has not been assessed. Therefore, this study investigates whether AHCC alleviates the side effects caused by chemotherapy in the patients with colorectal, lung, ovarian and pancreatic cancers.

**Study type:** Human clinical intervention trial.

**Study design:** Phase I/II clinical study: All patients received the first cycle of chemotherapy without AHCC and then did the second cycle with AHCC. Chemo-induced adverse effects and quality-of-life (QOL) of the patients was evaluated by blood tests, EORTC QLQ-C30 questionnaire, autonomic nerve function by acceleropedometer and DNA level of HHV-6 in saliva weekly. Reactivation of HHV-6 in saliva was examined for viral DNA by semiquantitative PCR method.

**Subjects:** 23 cancer patients.

**Dosage:** 3 grams of AHCC per day.

**Results:** AHCC supplementation resulted in the following changes:

- Improved hematologic toxicity (neutropenia) and hepatotoxicity
- A decreased tendency of QLQ-C30 fatigue scale
- A decrease in levels of HHV-6 in saliva by AHCC administration

**Conclusion:** "Taken together, our data suggested that AHCC could be safely administered with reduced adverse effects during chemotherapy, and further, the level of HHV-6 could be a good marker of QOL in such cancer patients."

*Biotherapy.*

Jang Seok Won. The hematoimmunologic effect of AHCC for Korean patients with various cancers. 2002 November; 16(6): 560-564.

**Topic:** Does AHCC have a hematoimmunologic effect on cancer patients?

**Background:** AHCC has immunomodulatory properties and is usually used as one of the complementary treatment agents for cancer patients. However, the mechanism of its antitumor effect is not clear. Therefore, subject is an "assessment" of AHCC's hematologic and cellular immunity effect was investigated in various cancer patients.

**Study type:** Human clinical intervention trial.

**Study design:** Open-label trial: Patients were administered AHCC for 9 months. A peripheral blood examination, including total leukocytes, peripheral lymphocytes, hemoglobin and hematocrit, was performed before AHCC administration and then every 3 months for a total of 3 times. Assessment of immune parameters was also performed before intake and then every 3 months after for a total of 2 times.

**Subjects:** 12 cancer patients.

**Dosage:** 3-6 grams of AHCC per day.

**Results:** AHCC supplementation resulted in the following changes compared with baseline:

- The ratio of NK cells to total lymphocytes increased from 21.67% before taking AHCC to 26.21% and 26.0% 3 to 6 months after taking AHCC, respectively
- There was no change in white blood cells, hemoglobin, hematocrit and thrombocyte numbers after taking AHCC, even though patients were undergoing radiotherapy or chemotherapy
- No adverse effects were observed

**Conclusion:** "This study suggests that AHCC can be used for the prevention of bone marrow depression and chemotherapy. Also, from the hematoimmunologic point of view, AHCC treatment seems to be safe and good for cancer patients, acting as a biological response modifier."

## Reduction of Chemotherapy Side-Effects

### *Biotherapy.*

Uno K, Kosuna K, Sun B, Fujii H, Wakame K, Chikumaru S, Hosokawa G, Ueda Y. Active Hexose Correlated Compound (AHCC) improves immunological parameters and performance status of patients with solid tumors. 2000 March; 14(3): 303-309.

**Topic:** Does AHCC have a biological response modifier (BRM)-like effect in advanced-stage cancer patients?

**Background:** Several medicinal compounds obtained from polysaccharide-rich plants are known to have BRM (biological response modifier) effects that enhance the immune system's antitumor effects. BRMs are substances that stimulate the body's response to infection and disease, including tumors. Because interleukin-12 (IL-12) and interferon- $\gamma$  (IFN- $\gamma$ ) negatively modulate tumor growth, the possible effect of AHCC on the production of IL-12 and IFN- $\gamma$  as well as NK cell activity (which also plays a critical role in cancer immunity) were investigated.

**Study type:** Human clinical intervention trial.

**Study design:** Open-label controlled trial: Subjects were administered AHCC for 6 months. NK cell activity in the peripheral monocytes and Th1 cytokine production (IFN- $\gamma$ , IL-12) were the immunological parameters investigated. Performance status (PS) as an indicator of quality of life was also measured. Each parameter was measured and evaluated 4 times, before AHCC and after administration of AHCC at 2 months, 4 months and 6 months.

**Subjects:** 38 cancer patients and 117 healthy people.

**Dosage:** 6 grams AHCC per day (in 3 doses after meals).

**Results:** AHCC supplementation resulted in the following changes compared with the status before intake:

- Significant improvement in NK cell activity
- Significant improvement in IFN- $\gamma$  and IL-2 production
- Significant improvement in PS evaluation

**Conclusion:** "The basal levels of 2 cytokines and NK activity in patients with tumors were lower than those in healthy people. All of 3 immunological parameters of patients increased to the normal levels after the intake of AHCC. These results demonstrate that AHCC improves both immunological abnormalities and clinical conditions."

*Presented at 2nd Meeting of the Society for Natural Immunity, May 1994.*

Ghoneum, M. NK-immunomodulation by AHCC in 17 cancer patients.

**Topic:** Does AHCC have an immunomodulating effect on cancer patients?

**Background:** Active hexose correlated compound (AHCC) is an enzyme-fermented extract of the basidiomycetes mushroom. The complex compound contains a mixture of polysaccharides, amino acids, lipids and minerals. The predominant components are oligosaccharides, totaling approximately 74% of the total dry weight. Of these, nearly 20% are partially acetylated  $\alpha$ -1,4-glucans, which are believed to constitute the active compounds in AHCC.

**Study type:** Human clinical intervention trial.

**Study design:** Open-label trial: Cancer patients with different advanced malignancies participated in the study. Patients received AHCC for 2–6 months. NK cell activity was examined by 4-hour Cr release assay against sensitive K562 and resistant Raji tumor cells.

**Subjects:** 17 cancer patients.

**Dosage:** 3 grams of AHCC per day.

**Results:** AHCC supplementation resulted in the following changes:

- Significant enhancement of NK activity against K562 as early as 2 weeks, two- to threefold increase compared with base line
- Activity was further increased at subsequent time periods up to 6 months post-treatment with AHCC
- NK activation was also detected against Raji cells, but at later stages 1-2 months with two- to ten fold increase compared with base line

**Conclusion:** "We conclude that AHCC is a potent immunomodulator and may be useful in immunotherapy of cancer."

## Hepatitis-C and Liver Disease

*The Medical News (Thailand).*

Thaiudom S, Piyaniran W, Chutaputthi A. A study of the efficacy of active hexose correlated compound (AHCC) in the treatment of chronic hepatitis C patients at Phramongkutklao Hospital (2010) 325, 13-16.

**Topic:** Does AHCC have an effect on patients with chronic hepatitis C?

**Background:** Hepatitis C virus (HCV) infection is an important issue worldwide, with over 170 million people infected with this virus. Generally, 2–35% of people infected with HCV will finally develop cirrhosis and hepatocellular carcinoma. Chronic hepatitis C patient treatment involves the use of pegylated interferon together with ribavirin. However, those regimens cause many side effects and are expensive. Previous research has shown that AHCC can improve natural killer (NK) cell macrophage function and increase the amount of several cytokines such as  $\gamma$ -interferon, IL-6 and TNF- $\alpha$ , which have antitumor properties. Also, AHCC can reduce the amount of HCV and serum alanine aminotransferase (ALT) levels, which may have an effect on the progression of the disease. Therefore, AHCC is being investigated for reducing HCV RNA levels and improving liver function.

**Study type:** Human clinical intervention trial.

**Study design:** Prospective, randomized, double-blind placebo-controlled trial: Patients received AHCC (n=19) or placebo (n=20) for 24 weeks. All patients received HCV RNA levels & liver function test monitoring. Also, the reduction of HCV RNA and ALT enzyme levels was observed.

**Subjects:** 39 chronic hepatitis C patients.

**Dosage:** 6 grams of AHCC per day.

**Results:** AHCC supplementation resulted in the following changes:

- Although no significant reduction of HCV RNA levels was noticed in AHCC group patients compared with those of placebo group, subgroup analysis of genotype-3 had a significant HCV RNA decline
- Although the reduction of ALT levels within AHCC group was not significant, a significant difference was found between AHCC and placebo groups
- AHCC group ALT levels were stable, while ALT levels increased in placebo group. Such difference was initially noted within the first 6 weeks of the study.

**Conclusion:** “Based on the result of this study, AHCC showed significant HCV RNA reduction in group B but not group A, and it could stabilize ALT levels when compared with placebo. This may delay the disease progression, providing patients more opportunities to receive any other treatment later on.”

*Presented at the 18th International Congress on Nutrition and Integrative Medicine (ICNIM), July 2010.*

Kim J. The Effect of AHCC in non-viral, chronic and abnormal liver function condition: a randomized, double-blind, placebo-control study. (2010).

**Topic:** Can AHCC improve liver function in patients with non-viral, chronic and abnormal liver function conditions?

**Background:** AHCC has demonstrated potential antitumor and immune modulating properties.

**Study type:** Human clinical intervention trial.

**Study design:** Randomized, double-blind, placebo-controlled: Subjects received AHCC or a placebo for 12 weeks. The inclusion criteria were one or more abnormal values among three liver function tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT) or  $\gamma$ -glutamyltransferase ( $\gamma$ -GT). Body weight, height, blood pressure, pulse rate and biochemical tests were measured after 4,8 and 12 weeks.

**Subjects:** 30 male subjects with non-viral, chronic and abnormal liver function conditions.

**Dosage:** 1 or 3 grams of AHCC per day.

**Results:** AHCC supplementation resulted in the following changes:

- 1 g AHCC significantly decreased AST, ALT and  $\gamma$ -GT values
- 3 g AHCC significantly decreased AST, ALT and  $\gamma$ -GT values except the 4-week  $\gamma$ -GT
- AHCC supplementation had a more dramatic effect on immune cell phenotypes after vaccination of subjects over 60 years old

**Conclusion:** “It was shown that the consumption of AHCC possessed beneficial effects on non-viral, chronic and abnormal liver function condition.”