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The effect of fermented soy (FSWW08) on blood hematology and cachexia in cancer patients

Abstract: In cancer patients, appetite and immune status are significantly weakened. Two experimental fermented formulations without (group A, named as FSWW08) and with (group B, FSWW08) an extract from yam root were investigated against a placebo formulation with casein (group C) in a clinical study conducted in six cancer hospitals where cancer patients underwent radio or chemotherapy (patients undergoing radiation therapy n=78, patients undergoing chemotherapy n=184, total 262). IgG and IgA were increased by formulation A in patients despite receiving radio- or chemotherapy. Group A experienced statistically significant increases in lymphocyte transformation rates, whereas group B and group C did not. Formulations A and B either inhibited or lessened statistically significant decreases in white blood counts, whereas the placebo group experienced substantial decreases. Hemoglobin and platelet decreases were inhibited in group A, although not statistically significantly. Patients in group A received no blood transfusions, whereas many patients from the placebo group received blood transfusions. Appetite loss was reduced in group A from 57.9% to 13.3% and in group B from 70% to 35.8%. In the placebo group, an increase in appetite loss was detected under chemo and radiation therapy from 41.8% to 70.9%.

Keywords: cachexial; cervical carcinoma; fermented soy; FSWW08; leukocytopenia; NF-κB; white blood counts.

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Introduction

Every year 13 million people worldwide are diagnosed with cancer, and 9 million people die from cancer [1]. Although cancer is a debilitating disease in and of itself, 40% of all patients die from such side effects as cachexia, fatigue and malabsorption [2, 3]. Chemotherapy and radiation treatment frequently increase these symptoms and lead to reduced treatment success. Both nutritional support [4] and drugs [5] are used by clinicians to improve nutritional wellbeing and organ status.

Tumors contain immune cells and a network of pro-inflammatory and anti-inflammatory cytokines, which collaborate in the development and progression of cancer [6]. Cytokine profiles may even prove to be prognostic [6]. It has been shown recently that cytokines from tumors can spread into the systemic blood stream (Figure 1) [8]. The systemic effects of pro-inflammatory cytokines are associated with fatigue, depression and cognitive impairment and can affect quality of life before, during and after treatment [9]. In people with advanced cancer, pro-inflammatory cytokines are additionally associated with anorexia, cachexia, pain, toxicity of treatment and resistance to treatment (Figure 1) [2, 3].

Recently, a research department of the US government showed that genistein, a substance found in soy, protects animals against leukocytopenia and reduces death rates that normally follow exposure to deadly radiation [10]. This was supported by Karamanos Hospital in Michigan [11–13], which revealed that several isoflavones can reduce radiation toxicity by increasing the number of white blood cells [14].

A specially fermented soy formulation, named FSWW08, increased body weight and appetite in several pilot trials [15, 16] and prolonged the survival of treatment-resistant cancer patients [15]. Therefore, a human study with a larger cohort of patients was designed to investigate the effect of two experimental fermented soy isoflavone formulations on symptoms of cachexia and leukocytopenia against a placebo formulation during chemotherapy and radiation therapy. FSWW08 (group A) was tested against a combination of FSWW08 with extract of yam root (group B) and a placebo formulation with casein (group c). The rationale of adding yam root extract came from in vitro studies showing that yam root extract may have a protective effect in cancer patients due to its cytotoxic effects on cancer cells [17–20].

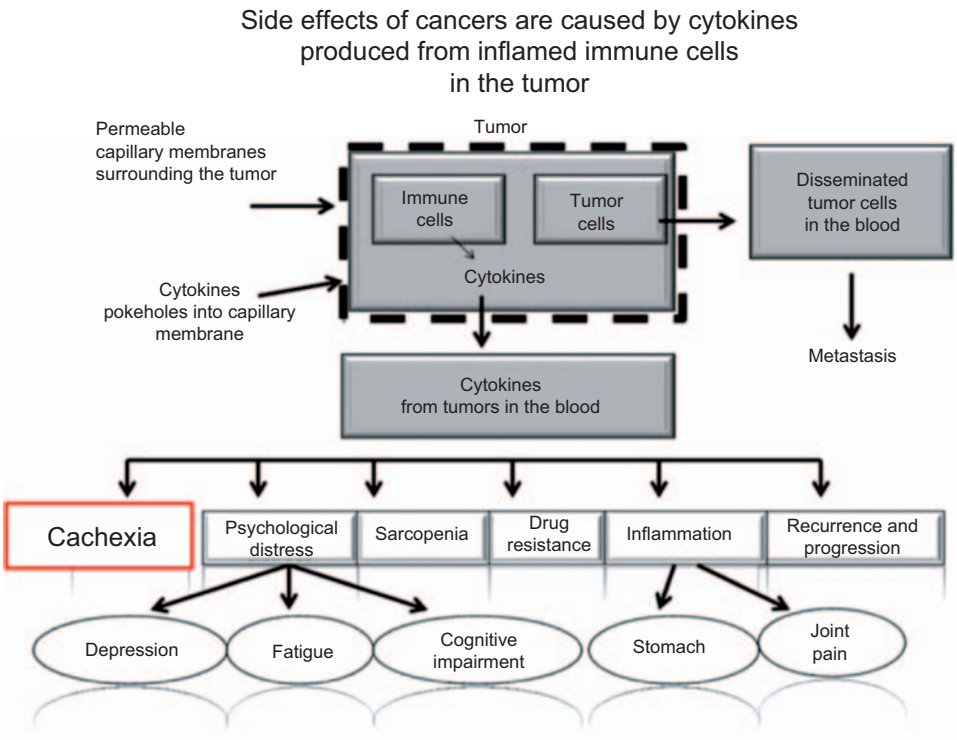

Figure 1 A conceptual model of cytokines in cancer.
Tumor and immune cells are sources of cytokines, which support the growth of cancer and lead to psychobehavioral symptoms (fatigue, depression and cognitive impairment), drug toxicity, drug resistance, anorexia and cachexia, pain and cancer recurrence and progression. Genetic background, cancer treatment and psychological distress can corroborate the production of cytokines. In cancer survivors, hyperactive immune cells might be the major source of cytokines in psychobehavioral symptoms [7].

Increased NF-κB (nuclear factor-kappaB) has been associated with many disease states, such as chronic inflammation, cancer, neurodegenerative disorders, diabetes and stroke (Figure 2) [21, 22]. In vitro and in vivo human studies on FSWW08 have shown it to have strong reductive effects on NF-κB in cancer cells (Table 1) [15], particularly in circulating cancer cells, a sub-fraction of cancer cells that may cause tumor spread and may define primary tumor activity [23] for which no type of chemotherapy or radiation currently shows any therapeutic efficacy [24]. Reduction of elevated NF-κB is therefore of tremendous clinical importance, silencing cancer cell activity while also reducing the elevated viral and

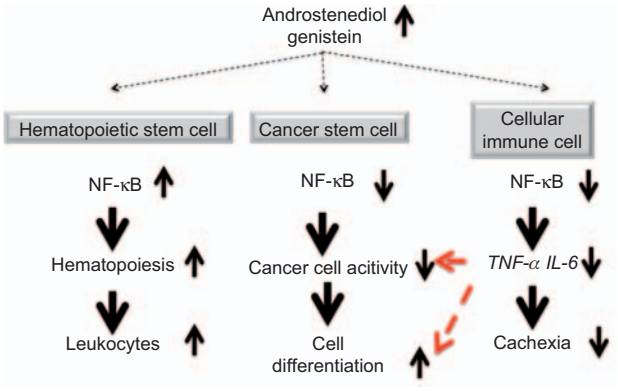

Figure 2 Schematic of the NF-κB role modulating activity of cancer cells, immune cells and hematopietic stem cells.

In vitro				
In vitro cell culture cancer cell line	Breast cancer BT474	Prostate cancer LNCaP	Liver cancer HepG2	Lung cancer LNCaP SW480
Decrease of Bcl_2/Bax ratio	−94%	−52%	−64%	−52%
In vivo				
Determined from extracted from blood circulating tumor cells from human cancer patients		Breast cancer −20%	Prostate cancer −94%	Ovarian cancer −80%
Decrease of Bcl_2/Bax ratio after 3 months of soy consumption				

Table 1 Comparison of Bcl_2/BAX ratio in cancer cells, an NF-κB surrogate marker.

bacterial infection risk observed in many cancer patients (Figure 2) [25]. Bone marrow-derived cells are the core constituents of both the innate and adaptive immune responses [26]. Proliferation, differentiation and apoptosis are the defining characteristics of hematopoiesis, and NF-κB participates in the regulation of each of these processes (Figure 2) [26]. Modulation of hematopoetic cells via NF-kB has been documented for B cell and T lymphocytes, but is also important for the development of NK cells, DCs, monocytes, granulocytes and other cellular components of the immune system [27–30] and may have general importance in the hematopoietic system (Figure 2).

NF-κB activation in cancer may be the result of either exposure to pro-inflammatory stimuli in the tumor microenvironment or up-regulation of the signaling pathway by upstream regulators (Figure 2) [26]. Appropriate control of NF-κB activity would provide a potential approach to managing NFκB-related tumors, the immunity of cancer patients and hematopoiesis (Figure 2) [26].

A key finding on FSWW08 from previous clinical studies is that soy isoflavones share many structural and pharmacological similarities with the adrenal hormone androstenediol (5-androstene-3b, 17b-diol), a direct metabolite of DHEA, such as 1) a protective effect against radiation damage in cancer treatment [31], 2) modification of NF-κB and 3) their function as estrogen receptor beta agonists [32]. FSWW08 increases functional steroidal hormones in patients, particularly androstenediol [33]. The “adiols”, androstenediol and androstanediol [a metabolite of testosterone via Dihydrotestosterone (DHT)], are strong modulators of Th1/Th2 cytokine balance, modifying immunity and providing strong anti-viral and anti-bacterial effects (Figure 3) [32–36]. Androstenediol, similarly to genistein, protects against radiation damage and facilitates hematopoiesis [31].

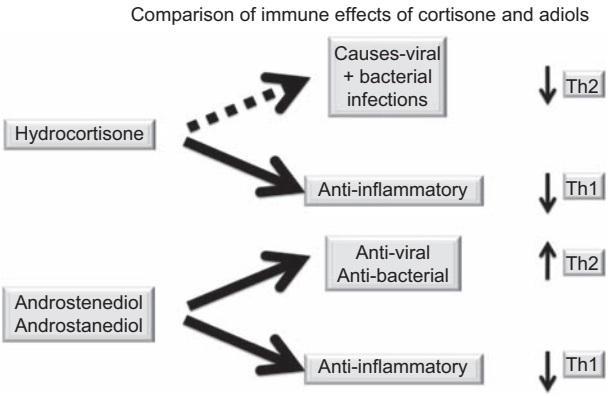

Figure 3 In vivo, the androstenes increase the levels of the Th1 cytokines, such as IL-2, IL-3 and IFN.
Similar to hydrocortisone, they suppress inflammation, but without immune suppression, and have a role in the maintenance of the Th1/Th2 balance and immune homeostasis. Taken from Ref. [32].

Subjects and methods

This study was approved by the University Hospital Institutional Review Boards and all participating local clinic institutional review boards of Fujian Medical College, Fuzhou, Fujian Province, Peoples Republic of China. Patients in cancer units were invited to participate in this trial. Exclusion criteria included diagnoses of severe mental disorders or diabetes mellitus, as well as inflammatory bowel disease, allergies to soy or other study product ingredients, pregnancy and consumption of soy products within the previous 30 days. Individuals who were not able to follow a doctor’s orders or who could not communicate with the treating physician were also excluded from the study.

A clinical study was conducted as a joint effort by six hospitals and one university medical school and was performed under the direction of the Fujian Provincial Department of Public Health and the Fujian Medical College, Fujian, Peoples Republic of China as a joint study with the following hospitals:

- Concord (Xiehe) Hospital, affiliated with Fujian Medical College
- No. 1 Hospital, affiliated with Fujian Medical College
- Fuzhou General Hospital of Nanjing Military District
- Fuzhou Pulmonogy Hospital, Fuijan, Peoples Republic of China
- Provincial Coal Mine Sanatorium, Fuijan, Peoples Republic of China

Before conducting the study, an ethics vote was obtained by the Fujian Provincial Department of Public Health.

The aim of the study was to investigate the benefits of two liquid fermented soy formulations compared to a placebo liquid formulation for cancer patients receiving standard chemotherapy or standard radiotherapy in these hospitals. The study included 262 cancer patients: 184 receiving chemotherapy and 78 receiving radiation therapy (Table 2).

Study design

We conducted a randomized, double-blind, placebo-controlled, early-phase trial. Cases were selected in accordance with an established protocol. Informed consent was obtained from all participants. Patients were medically diagnosed with cancer, and their condition was confirmed either by surgical operations and/or pathology, cytology or CT scanning. Patients with and without surgical operations were all chosen as potential candidates. Three different groups were established. Patients were assigned randomly to the two soy supplement arms or to the placebo arm. Standard chemotherapy or radiation therapy was conducted in these hospitals. After 3 months, the patients were reevaluated.

	Groups	Radiotherapy				Chemotherapy			
		A	B	Placebo	Total	A	B	Placebo	Total
	No of cases	34	27	17	78	70	67	47	184
Sex	Male	29	20	12	61	45	47	32	124
	Female	5	7	5	17	25	20	15	60
Age		48.1±14.5	47.6±15.9	45.5±14.5		59.9±14.2	55.2±11.6	54.9±11.3	
Cancer	Type								
Distribution	Head and Face	8	2	1	29	16	14	2	32
	Neck	0	1	0	1	1	1	0	2
	Abdomen	5	6	6	17	27	13	8	58
	Chest	13	10	3	26	23	19	17	59
	Others	10	8	7	25	15	9	9	33
Surgery	No	28	20	9	57	27	25	17	69
	Yes	6	8	8	20	43	42	29	114
Course (weeks)	<4	0	1	0	1	0	13	1	14
	4 or more	8	16	17	41	18	11	18	47
	6 or more	14	11	0	25	6	7	3	16
	8 or more	12	0	0	12	46	36	25	107

Table 2 Comparisons of patient characteristics receiving A) FSWW08, a fermented soy solution, B) FSWW08 with yam root extract or C) a casein placebo formulation, in patients receiving either radiotherapy or chemotherapy.

Drug formulation

Treatment was a 220-mL fermented soy shake (provided by Haelan, Inc., Woodinville, WA, USA), that contained approximately 700 mg of soy isoflavones per serving in both formulations. Additionally, the formulation contained the Bowman Birk Inhibitor Factor, a protease inhibitor with anticancer activity in humans [21, 37]. This formulation is named FSWW08.

Participants in group A received this formulation. A newly developed 80-mL soy formulation that also contained yam root extract and other polyphenols (by Haelan, Inc.) was tested on participants in group B. Participants in the placebo group received a commercially available 80-mL casein shake. The flavoring of the two fermented soy supplements was identical. No sweetening or improvement in taste was undertaken in any of these formulations.

Clinical laboratory parameters

The EQRTC QLQ-C30 (Version 1) is a validated questionnaire that was developed for cancer patients, with particular regard to common side effects. This questionnaire contains 30 questions, most of which are to be answered in terms of four levels, running from no effect up to extremely difficult. The EORTC QLQ-C30 (Version 1) was filled out by patients in all three groups prior to chemo or radiation therapy and following 3 months of therapy.

Blood chemistry

The following blood markers were determined by drawing blood through the antecubital vein: liver inflammation marker alanine transaminase (ALT), as well as white blood count (WBC), neurogranulocyte count, blood platelets (Pt), hemoglobin (Hb) lymphocyte transformation rate (LCT), immune globulin G (IgG), immune globulin (M) and immune globulin (A).

Examination of general health

Prior to treatment, a complete medical examination was given to all patients enrolled in the trial. A case history was recorded each week before the beginning of the testing procedure. One week after nutritional supplementation, a complete reexamination and evaluation was performed.

General information

The distributions of cancer in this group of patients were as high as 23 varieties. The number of cancers were higher than the number of participants included in the study, as patients sometimes suffered from a primary tumor and a follow-up tumor and metastasis. Common cancers were as follows:

- Stomach: 69 cases (chemotherapy)
- Esophagus: 25 cases (chemotherapy in seven cases; radiotherapy in 17 cases)
- Lung: 51 cases (chemotherapy in 48 cases; radiotherapy in three cases)
- Nasopharynx: 34 cases (chemotherapy in five cases; radiotherapy in 29 cases)
- Intestinal: 51 cases (chemotherapy in 50 cases; radiotherapy in 1 case)
- Acute lymphoma: 51 cases (chemotherapy in 34 cases; radiotherapy in 17 cases)
- Acute granulocytemia: 12 cases (chemotherapy)

Statistical analysis

Basic demographic and clinical results were tested with Student's t-test and the F-test. Statistical differences between groups were calculated either by one-way analysis of variance (ANOVA) followed by a Fisher's LSD post hoc test or by a Fisher's exact test. Differences were considered significant if $p<0.05$.

Case report

The subject of the single case report was treated in Mainz, Germany. A Caucasian cervical cancer patient was referred to our private practice, and her case is reported here. Clinical records are of this patient and are summarized in Figure 4.

Results

Baseline characteristics

A total of 264 patients were enrolled in the study (Table 2). Median age and standard deviation in radiation therapy and chemotherapy in the different groups were quite comparable and did not differ to any statistically significant extent. About one-third of study participants were female, and two-thirds were male.

In contrast to the situation in Western cancer centers, breast and prostate cancer incidences were almost negligible; other types of cancers predominated (Table 2). In the radiation treatment group, the majority of cancer patients received 4–6 weeks of cancer treatment, whereas in the chemotherapy treatment group, patients spent over 8 weeks undergoing therapy.

Cachexia

As shown in Table 3 the most frequent symptoms described by patients during radiation and chemotherapy treatment were decreased appetite (57.98%) and nausea and vomiting (34.45%). Following nutritional supplementation with the two fermented soy formulations, decreased appetites in the two groups reversed substantially, whereas an increase was detected in the placebo group. Nausea and vomiting effects were reduced from 34.45% to 6.7% in group A, whereas they decreased from 40% to

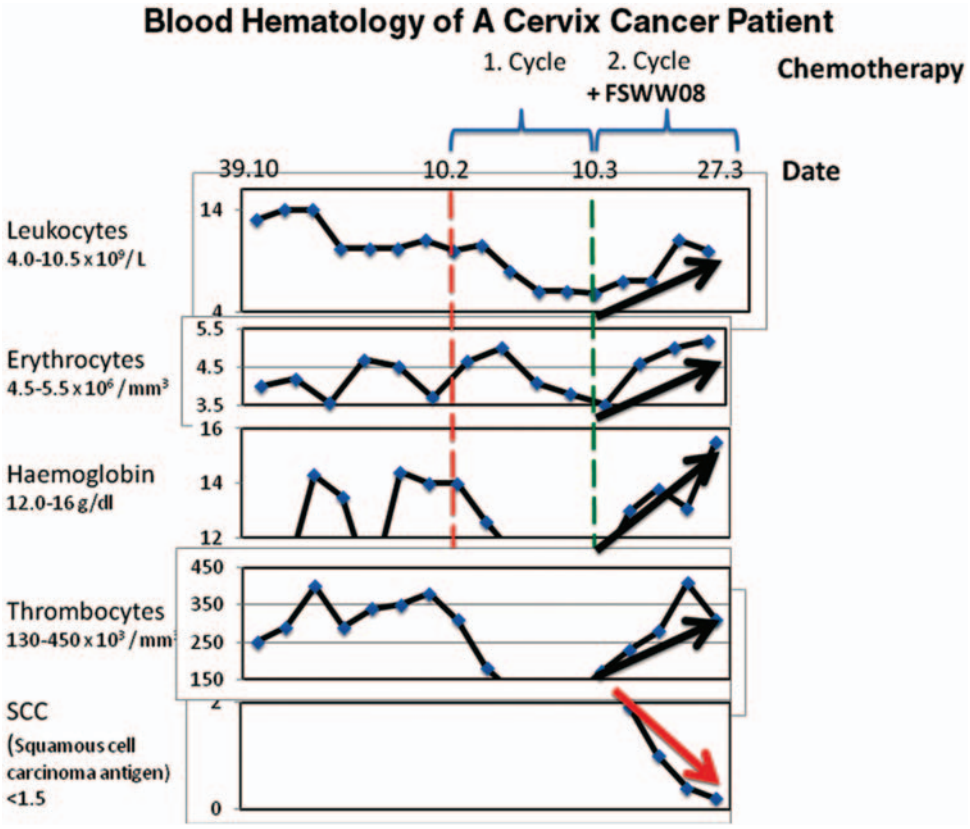

Figure 4 Time course of individual blood hematology marker and their normal range for cervical cancer patient ES. The patient received two rounds of cycle Cisplatin/Topotecan. Additionally, the patient consumed FSWW08 daily in the middle of treatment cycle 2. Tumor marker SCC denotes squamous plate epithelial carcinoma antigen.

Group		A			B			Placebo	
	n 104	Before treatment	After treatment	n 94	Before treatment	After treatment	n 74	Before treatment	After treatment
Appetite loss									
0		35	88		36	67		36	11
I		44	12		31	26		25	23
II		16	3		21	7		12	37
III		9	1		6	1		2	3
Nausea and vomiting									
0		63	92		43	61		43	17
I		19	6		20	17		9	32
II		19	6		20	15		9	12
III		3	0		7	1		3	3
Diarrhea									
0		92	103		75	89		56	57
I		8	0		9	5		4	6
II		4	0		8	0		4	1
III		0	1		2	0		0	0
Constipation									
0		103	103		88	84		54	50
I		0	1		4	8		10	13
II		1	0		2	2		0	1
III		0	0		0	0		0	0
Hair loss									
0		93	100	94	88	80	64	57	39
I		8	3		5	8		7	16
II		3	1		1	5		0	9
III		0	0		0	1		0	0
Stomatitis									
0		87	103		88	91		58	49
I		14	1		5	3		1	8
II		3	0		1	0		5	7
III		0	0		0	0		0	0

Table 3 Effects of fermented soy formulation FSWW08 in cancer patients, without A) or with B) yam root extract and C) a placebo formulation with casein on symptoms associated with radiation therapy and chemotherapy.
Symptoms were graded individually by the EQRTC QLQ-C30 (Version1).

20% in group B; in the placebo group, a strong, almost 3-fold increase from 22.78% to 60% was observed. The fermented soy preparation did not inhibit alopecia, as hair loss was similar in groups A and B and the placebo group. Diarrhea was reduced in group A and less pronouncedly reduced in group B, whereas no effect was detected in the placebo group. Hemorrhaging was reduced in groups A and B, whereas the placebo group showed no statistically significant effect. Stomatitis increased significantly in the placebo group, but not in groups A or B.

Immune function

Results show that IgG and IgA were within the normal range under consumption of formulation A for both radiation and chemotherapy (Table 4). Patients in group A experienced elevated lymphocyte transformation rates, whereas these were less elevated in group B, and patients experienced a statistically significant decrease in the placebo group (Table 4).

WBC (leukocytes)

The number of WBCs was reduced in the placebo and in the radiation group, although statistically not significantly (Table 5). The placebo group that received chemotherapy showed substantial decreases in WBCs, with almost 50% of patients being below the normal range, whereas both fermented soy formulations prevented a decrease in WBCs uring chemotherapy (Figure 5). Therefore, several patients in the placebo group received blood transfusions, as well as five in the chemotherapy group (=23%) and four in

			Radiotherapy			Chemotherapy		
			n	Before treatment	After treatment	n	Before treatment	After treatment
IgG, g/L	A	X±s	34	12.5±2.9	13.7±2.7	70	11.2±3.1	12.2±2.8[a]
	B		27	14.9±5.6	15.9±4.25	66	11.7±3.0	12.8±3.5[a]
	Placebo		17	15.4±2.7	14.3±1.7	47	11.2±3.3	11.2±3.8
IgA, g/L	A	X±s	34	3.5±2.1	3.5±1.6	70	2.0±1.0	2.3±1.1[a]
	B		27	2.8±1.3	3.4±1.2	66	2.2±1.0	2.2±1.1
	Placebo		17	3.7±1.4	3.6±1.0	47	1.8±0.6	1.8±0.6
IgM, g/L	A	X±s	34	1.4±0.6	1.5±0.6	70	1.5±0.8	1.7±0.7
	B		27	1.8±0.7	1.8±0.4	66	1.6±1.3	1.6±1.3
	Placebo		17	2.1±0.7	1.9±0.4	47	1.5±0.6	1.5±0.5
LCT, %	A	X±s				35	30.3±9.6	53.7±11.8[a]
	B					20	46.4±7.4	53.7±6.1[b]
	Placebo					20	51.0±7.8	47.7±10.0

Table 4 Comparison of immune parameters in three patient groups before and after treatment with FSWW08, a formulation similar to FSWW08 with yams, or a casein placebo formulation.
Before treatment and after, [a]p<0.01 and [b]p<0.05.

the placebo group undergoing radiation therapy (=8.5%) (Figures 5 and 6). None of the patients from group A and only one from group B received a blood transfusion.

Hemoglobin (Hg) and Platelets (Pt)

The cancer patients who received the fermented soy solutions (group A and B) showed a small decrease in hemoglobin (Hg) as they underwent radiation therapy, whereas the placebo group showed a substantial decrease in Hg (Table 5). No change was detected in either of the groups combining fermented soy solutions with chemotherapy. The placebo group did show a substantial decrease when chemotherapy was performed. No change in Pt count was detected in any of the groups.

Case report

E.S. was born in 1955. A carcinoma of the cervix was diagnosed in 1983, and it was necessary to perform a

			Radiotherapy			Chemotherapy		
			n	Before treatment	After treatment	n	Before treatment	After treatment
WBC ($\times 10^9$/L)	A	x±s	34	6.93±3.10	5.98±1.41	70	6.25±1.94	6.23±1.41
	B		27	7.05±3.34	5.98±1.49	67	5.85±2.08	5.74±1.67
	Placebo		17	6.41±1.90	4.72±9.94	47	5.71±1.71	4.42±1.15
	A:Placebo	(d):(d)			0.562[a]: −1.683			−0.027[a]: −1.829
	B:Placebo				−0.111[b]: −1.683			−0.196[c]: −1.829
Hb ($\times 10^9$/L)	A	x±s	34	4.33±1.48	4.08±1.01	70	4.08±1.19	4.26±2.55
	B		27	4.61±2.99	4.20±1.12	67	3.53±1.19	3.45±1.26
	C		17	4.23±1.57	3.88±9.74	47	3.73±1.10	2.83±2.13
	A:Placebo	(d):(d)			0.278[b]: −0.805			0.15[a]: −1.074
	B:placebo				−0.399: −0.805			−0.19[c]: 1.074
Pt ($\times 10^9$/L)	A	x±s	34	187±62.5	194±52.7	70	158±68.1	160±100
	B		27	176±54.9	181±29.0	67	134±68.1	139±64.9
	Placebo		17	213±51.4	185±35.3	47	139±62.5	613±35.0

Table 5 Comparison of blood hematology of A) a fermented soy formulation FSWW08, B) FSWW08 with yam root extract and C) a placebo formulation with casein.
Treatment effects: [a]p<0.001. [b]p<0.05. [c]p<0.01.

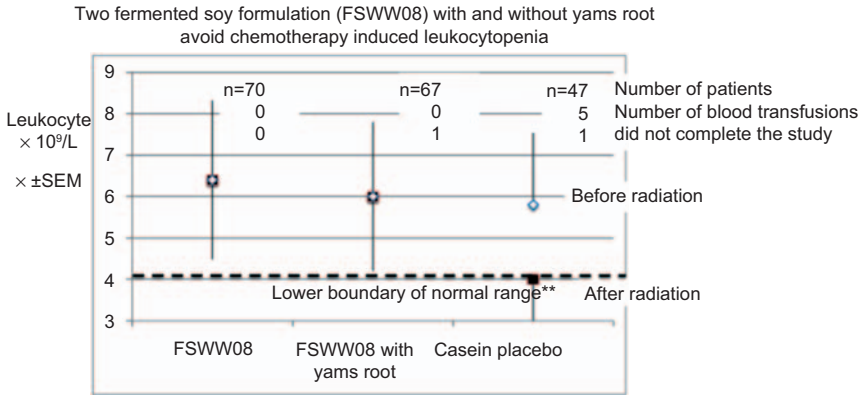

Figure 5 Mean and standard deviation of leukocytes before (grey-filled squares) and after (black-filled squares) chemotherapy with FSWW08, or FSWW08 with yam root extract or a casein placebo solution.
Dashed line limits lower range of normal range. **Denotes a statistically significant difference on the $p<0.01$ error level of significance.

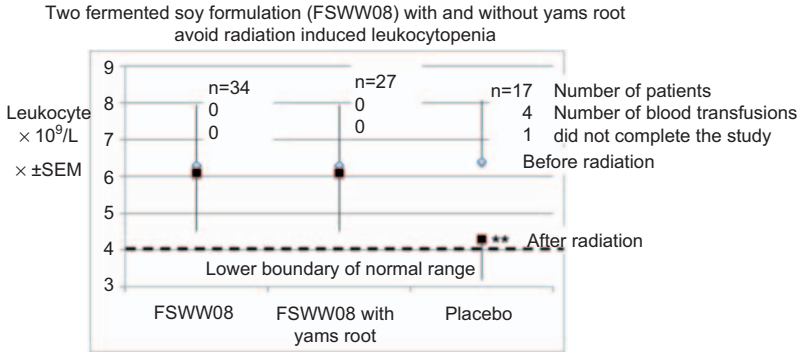

Figure 6 Mean and standard deviation of leukocytes before (grey-filled squares) and after (black-filled squares) radiation with FSWW08, or FSWW08 with yam root extract or a casein placebo solution.
Dashed line limits lower range of normal range. **denotes a statistically significant difference on the $p<0.01$ error level of significance.

Wertheim-Meigs surgery with postsurgical radiation that same year. A Wertheim-Meigs surgery entails the removal of gynecological organs with a radical hysterectomy, but also a lymphatic adenectomy with removal of connective tissue and lymph nodes in the pelvis medial and lateral of the arteria or vena ilaca communis. Additionally, the paracolpicum of the Fossa obturatoria up to the pelvis was removed. The radiation caused a large rectum-vaginal fistula and induced fibrosis, eventually making stoma surgery necessary in 2005 (Table 6).

Blood analysis revealed an increase of CRP and a leukocytosis of 11.600/nL. The patient, whose record is summarized in Table 3, suffered a fate that is typical of late-stage cancer patients: at the point of tumor diagnosis, the patient had already suffered tremendous weight loss and was very fragile. Under the first cycle of chemotherapy, all blood hematology parameters decreased (Figure 4). This was corroborated by the fact that the patient's general health deteriorated even more; eventually an ambulance was called, and she was admitted to the intensive care unit. Ten days before the second cycle of chemotherapy, daily fermented soy supplementation (FSWW08) was initiated. Blood hematology improved immediately, corroborated by an improvement in general health and an increase in body weight (Table 6, Figure 4). Several months later, another round of follow-up surgery was necessary. At that point, she was diagnosed cancer-free.

Discussion

Pharmaceutical researchers and clinicians have discussed adding natural compounds to improve the efficacy and reduce side effects of cancer treatment [38]. A department of the US Military in charge of protecting humans against radiation fallout from nuclear weapons has shown in animal studies that consumption of the isoflavone genistein protects mice against a deadly dose of radiation in a laboratory setting [10].

Oct 21, 2005	Stoma surgery –poor general health condition –after hospital discharge, body weight only 41 kg –tremendous postsurgical wound infection with secondary wound healing after stoma surgery
Feb 12, 2006	Diagnosis of a cervical cancer stadium IVa
Feb 14, 2006	Nephrostomy surgery, which was necessary to protect the patient against cytotoxicity against chemotherapy
Feb 20, 2006	Received one cycle chemotherapy (Cisplatin/Topotecan) –extreme poor general health condition –nausea and vomiting –no appetite (cachexia) –emergency call for an ambulance
March 10, 2006	10 days before second cycle of chemotherapy –started administration of fermented soy (Haelan 951) –no toxic side effects –steady increase in body weight –substantial improvement of blood hematology –excellent general health
June 29, July 06, Aug 7, 2006	MRT was performed Ms. E.S. was diagnosed as cancer-free 11-h surgery: colon conduit is performed (and elimination of nephrostomy). After surgery, no wound healing problems were detected Tissue samples show no cancer cells Patient was still under FSWW08 nutrition

Table 6 Case report of the cervical cancer patient E.S., born 1955.

The clinical study presented here shows that the use of two fermented soy products (FSWW08 with and without yam root extract) reduces appetite loss, cachexia and leukocytopenia in cancer patients undergoing chemotherapy or radiotherapy. In contrast to this finding, patients who received a placebo solution showed substantial increases in appetite loss and leukocytopenia under both radiotherapy and chemotherapy, symptoms that are seen routinely in cases where chemotherapy or radiation therapy is conducted. The addition of extract from yam root extract did not affect a statistically significant improvement in clinical results. One reason, among others, may be that yams have a mechanism similar to soy. Extracts of yam root are capable of having cytotoxic effects on cancer cells, which is different from the direct effect of isoflavones. However, as human studies have shown, FSWW08 is capable of increasing estradiol, and other human studies have shown that 2-hydroxy-metabolites and 4 hydroxy-metabolites are increased by soy consumption: As a consequence, 2-methoxyestradiol is increased by soy consumption, which shows strong anti-angiogenesis and cytotoxic effects [39]. Therefore, it cannot be excluded that the cytotoxic effects of yam root extract in cancer cells as shown by in vitro experiments [18] may still be identified in additional clinical experiments where only yam root extract is tested in cancer patients.

Patients participating in this study underwent standard chemotherapy or radiotherapy regimens in China, which entailed a lower number of cancers typically seen in the Western world: No breast or prostate cancer patients were enrolled in this study. A clinical study investigating the efficacy of FSWW08 in Caucasians suffering from prostate, breast and ovarian cancer, the results of which were reported elsewhere [15], also revealed strong anticachectic effects [9].

The case report presented here indicates that FSWW08 shows hematopoietic effects in Caucasian cancer patients: substantial improvement in blood hematology was observed (Figure 5), corroborating animal experiments reported in the literature [10]. Presently, there can only be speculation about what causes this effect. However, cell differentiation in tissues is inhibited by inflammatory cytokines [6]. As FSWW08 clinically improves the immunity of cancer patients, reducing inflammatory cytokines, it may have strong effects on blood hematology, as has been reported in the literature regarding the soy component genistein.

Studies of FSWW08 improving survival in various cancers in Caucasian women after have been reported [15]. The improvement in nutritional status may very well increase survival. However, in addition to improving nutritional status, FSWW08 also has a strong effect on the genome of cancer cells, in particular improving NF-kB, which influences immunity and, as a consequence,

Th1-cytokine formation [16]. Therefore, the improvement of blood hematology and cachexia may very well be related to improvement in cancer treatment.

Soy consumption has been reported in the literature to have many beneficial effects on bone health, the cardiovascular system and degenerative arthritis and has been shown in epidemiologic studies to be associated with a lower risk of several cancers [38]. In light of interesting findings from animal studies [10] and human studies [9, 15, 16], a study was initiated to investigate whether a soy product, FSWW08, would increase hematopoiesis and increase appetite in cancer patients.

Among other ingredients, FSWW08 contains isoflavones, saponins, amino acids and the protease inhibitor Bowman Birk Inhibitor [15], a strong immune modulating factor that has been shown to have strong anti-cancer effects in humans [21]. Therefore, FSWW08's effect in humans cannot be attributed solely to isoflavones. This point needs to be investigated in larger clinical trials.

Increases in hematopoietic stem cell activity by isoflavones in the bone marrow compartment can be facilitated by altering NF-κB (Figure 2) [38]. Reduction of cachexia in cancer patients may be caused by cytokine formation of cancer stem cells in cancer tissue (Figure 1) [6]. This, however, is mediated by a decrease in NF-κB activity of tumor cells [9, 15, 16].

Increased NF-κB plays an important role during the endothelial response to inflammatory stress and facilitates tumor growth into endothelial cells [21]. Cancer stem cells do express NF-κB and could very well be silenced via inhibition of NF-κB [21]. This is very important as cancer stem cells do not express hormone receptors and cannot be modulated via this pathway [34, 40]. Most importantly, cancer stem cells are unresponsive to chemotherapy or radiation [24] but may respond via NF-κB.

The human estrogen receptor beta (ER-ß) agonist androstenediol (or adiol) is metabolized from DHEA. Adiol has been shown to increase hematopoietic stem cell activity [31], to reduce cytokines in peripheral stem cells and to be a very potent immunomodulator [31–36, 41]. In addition to sharing receptor affinities and pharmacological effects, adiol and soy isoflavones elicit similar effects in humans: in particular, they are both ER-β agonists and both have also shown beneficial effects on bone formation during adolescence [7, 42] as well as blood formation. In the bone marrow compartment, adiol facilitates bone formation by increasing both the amount of NF-κB (the bone formation factor RANKL must be viewed as a bone-specific NF-κB) and blood formation (Figure 2) [31]. Adiols reduce infection and inflammation, although they are not antiviral drugs like acyclovir or similar drugs, which act directly on the replication of the virus [32]. Adiols act indirectly by modifying the Th1/Th2 balance and modifying macrophage activity and immunity (Figure 2) [32]. As was seen in all studies investigating FSWW08, it did reduce viral and bacterial infections in cancer patients [9, 15, 16].

Cachexia in cancer patients is caused by an increase of Th1-cytokine in the blood compartment. Th1-cytokines are formed in the tumor and then then released from the tumor into the peripheral blood compartment (Figure 1) [2–4, 6]. Cytokine formation in immune cells in the tumor is mediated by NF-κB (Figure 2). It has been shown in several human studies, as well as with in vitro cells, that FSWW08 is capable of reducing NFkB and Th1-cytokines, such as TNF-α [16].

In addition to an improvement in clinical parameters, this study shows that life-maintaining procedures like blood transfusions in cancer patients could be avoided using fermented soy (FSWW08).

This study shows that FSWW08 can affect statistically significant improvements in both cachexia and the blood hematology of cancer patients undergoing chemotherapy and radiotherapy, corroborating animal experiments. The body of evidence is mounting that soy isoflavones may have positive effects particularly on human stem cells and in bone, blood, nerve and cancer stem cells [33]. Interestingly, the ability of soy isoflavones to alter stem cells in humans may be derived from their function in plants [43].

Additional studies in a larger patient cohort are warranted.

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References

1. Fonkych K, O'Leary JF, Melnick GA, Keeler EB. Medicare HMO impact on utilization at the end of life. Am J Manag Care 2008;14:505–12.
2. Morley JE, Thomas DR, Wilson MM. Cachexia: pathophysiology and clinical relevance. Am J Clin Nutr 2006;83: 735–43.
3. Kotler DP. Cachexia. Ann Intern Med 2000;1333:622–34.
4. Mantovani G, Macciò A, Madeddu C, Gramignano G, Serpe R, Massa E, Dessì M, Tanca FM, Sanna E, Deiana L, Panzone F, Contu P, Floris C. Randomized phase III clinical trial of five different arms of treatment for patients with cancer cachexia: interim results. Nutrition 2008;24:305–13.
5. Tassinari D, Santelmo C, Tombesi P, Sartori S. Thalidomide in the treatment of cancer cachexia. J Palliat Care 2008;24:187–9.

6. Seruga B, Zhang H, Bernstein LJ, Tannock IF. Cytokines and their relationship to the symptoms and outcome of cancer. Nat Rev Cancer 2008;8:887–99.
7. Remer T, Boye KR, Hartmann MF, Wudy SA. Urinary markers of adrenarche: reference values in healthy subjects, aged 3–18 years. J Clin Endocrinol Metab 2005;90:2015–21.
8. Atanackovic D, Cao Y, Kim JW, Brandl S, Thom I, Faltz C, Hildebrandt Y, Bartels K, de Weerth A, Hegewisch-Becker S, Hossfeld DK, Bokemeyer C. The local cytokine and chemokine millieu within malignant effusions. Tumor Biol 2008;29: 93–104.
9. Jacob U, Gocan A, Bachg D, Rohr UD. Applikation von fermentierter Soja bei Krebspatienten zur Verminderung von Kachexie und Erhöhung der Apoptose – eine prospektive Pilotstudie. J Gynecol Endokrinol 2009;19:18–28.
10. Day RM. Genistein protects against biomarkers of delayed lung sequelae in mice surviving high doses of total body irradiation. Radiat Res 2008;46:361–72.
11. Sarkar FH, Li Y. NF-kappaB: a potential target for cancer chemoprevention and therapy. Front Biosci 2008;13:2950–9.
12. Raffoul JJ, Banerjee S, Singh-Gupta V, Knoll ZE, Fite A, Zhang H, Abrams J, Sarkar FH, Hillman GG. Down-regulation of apurinic/apyrimidinic endonuclease 1/redox factor-1 expression by soy isoflavones enhances prostate cancer radiotherapy in vitro and in vivo. Cancer Res 2007;67:2141–9.
13. Raffoul JJ, Wang Y, Kucuk O, Forman JD, Sarkar FH, Hillman GG. Genistein inhibits radiation-induced activation of NF-κB in prostate cancer cells promoting apoptosis and G2/M cell cycle arrest. Cancer Res 2007;67:2141–9.
14. Zhou Y, Mi MT. Genistein stimulates haematopoeis and increases survival of irradiated mice. J Radiat Res 2005;46:425–33.
15. Gocan AG, Bachg D, Schindler AE, Rohr UD. Managing immunity in resistant cancer patients correlates to survival: results and discussion of a pilot study. Horm Mol Biol Clin Invest 2011;8:455–69.
16. Rohr UD, Gocan AG, Bachg D, Schindler AE. Cancer protection of soy resembles cancer protection during pregnancy. Horm Mol Biol Clin Invest 2010;3:391–409.
17. Shu D, Qing Y, Tong Q, He Y, Xing Z, Zhao Y, Li Y, Wei Y, Huang W, Wu X. Deltonin isolated from Dioscorea zingiberensis inhibits cancer cell growth through inducing mitochondrial apoptosis and suppressing Akt and mitogen activated protein kinase signals. Biol Pharm Bull 2011;34:1231–9.
18. Saekoo J, Dechsukum C, Graidist P, Itharat A. Cytotoxic effect and its mechanism of dioscorealide B from Dioscorea membranacea against breast cancer cells. J Med Assoc Thai 2010;93(Suppl 7):S277–82.
19. Jaiaree N, Itharat A, Kumapava K. Cytotoxic saponin against lung cancer cells from Dioscorea birmanica Prain & Burkill. J Med Assoc Thai 2010;93(Suppl 7):S192–7.
20. Liu H, Chou GX, Wang JM, Ji LL, Wang ZT. Steroidal saponins from the rhizomes of Dioscorea bulbifera and their cytotoxic activity. Planta Med 2010;77:845–8.
21. Kumar A, Takada Y, Boriek AM, Aggarwal BB. Nuclear factor-kappaB: its role in health and disease. J Mol Med 2004;82:434–48.
22. Baldwin AS, Jr. Series introduction: the transcription factor NF-kappaB and human disease. J Clin Invest 2001;107:3–6.
23. Liu S, Ginestier C, Ou SJ, Clouthier SG, Patel SH, Monville F, Korkaya H, Heath A, Dutcher J, Kleer CG, Jung Y, Dontu G, Taichman R, Wicha MS. Breast cancer stem cells are regulated by mesenchymal stem cells through cytokine networks. Cancer Res 2011;71:614–24.
24. Baker M. Stem cells: fast and furious. Nature 2009;458:962–5.
25. Nogueira L, Ruiz-Ontañon P, Vazquez-Barquero A, Moris F, Fernandez-Luna JL. The NFκB pathway: a therapeutic target in glioblastoma. Oncotarget 2011;2:646–53.
26. Hayden MS, Ghosh S. NF-κB in immunobiology. Cell Research 2011;21:223–44.
27. Tang M, Wei X, Guo Y, Breslin P, Zhang S, Zhang S, Wei W, Xia Z, Diaz M, Akira S, Zhang J. TAK1 is required for the survival of hematopoietic cells and hepatocytes in mice. J Exp Med 2008;205:1611–9.
28. Goudeau B, Huetz F, Samson S. IkappaBalpha/Ikappa-Bepsilon deficiency reveals that a critical NF-kappaB dosage is required for lymphocyte survival. Proc Natl Acad Sci USA 2003;100:15800–5.
29. Liu K, Victora GD, Schwickert TA. In vivo analysis of dendritic cell development and homeostasis. Science 2009;324:392–7.
30. Li Y, Wicha MS, Schwartz SJ, Sun D. Implications of cancer stem cell theory for cancer chemoprevention by natural dietary compounds. J Nutr Biochem 2011;22:799–806.
31. Xiao M, Inal CE, Parekh VI, Chang CM, Whitnall MH. 5-androstenediol promotes survival of gamma-irradiated human hematopoetic progenitors through induction of nuclear factor-kappaB activation and granulocyte colony-stimulating factor expression. Mol Pharmacol 2007;72:370–9.
32. Loria RM. Beta-androstenes and resistance to viral and bacterial infections. Neuroimmunomodulation 2009;16:88–95.
33. Gocan AG, Bachg D, Schindler AE, Rohr UD. Balancing steroidal hormone cascade in treatment-resistant veteran soldiers with PTSD using a fermented soy product (FSWW08): a pilot study. Horm Mol Biol Clin Invest 2012;10:301–14.
34. Roth TM, Ramamurthy P, Muir D, Wallace MR, Zhu Y, Chang L, Barald KF. Influence of hormones and hormone metabolites on the growth of Schwann cells derived from embryonic stem cells and on tumor cell lines expressing variable levels of neurofibromin. Dev Dyn 2008;237:513–24.
35. Szalay L, Shimizu T, Suzuki T, Hsieh YC, Choudhry MA, Schwacha MG, Bland KI, Chaudry IH. Androstenediol administration after trauma-hemorrhage attenuates inflammation response, reduces organ damage, and improves survival following sepsis. Am J of Physiol Gastrointest Liver Physiol 2006;291:G260–6.
36. Singh VK, Grace MB, Jacobsen KO, Chang CM, Parekh VI, Inal CE, Shafran RL, Whitnall AD, Kao TC, Jackson WE 3rd, Whitnall MH. Administration of 5-androstenediol to mice: pharmacokinetics and cytokine gene expression. Exp Mol Pathol 2008;84:178–88.
37. Kennedy AR. Chemopreventive agents: protease inhibitors. Pharmacol Ther 1988;78:167–209.
38. Sakai T, Kogiso M. Soy isoflavones and immunity. J Med Invest 2008;55:167–73.
39. Fuhrman BJ, Pfeiffer, Xu X, Wu AH, Korde L, Gail MH, Keefer LK, Veenstra TD, Hoover RN, Ziegler RG. Soy intake is associated with an increased 2-hydroxylation and decreased 16α-hydroxylation of estrogens in Asian-American women. Cancer Epidemiol Biomarkers Prev 2009;18:2751–60.
40. Haddad PS, Azar GA, Groom S, Boivin M. Natural health products, modulation of immune function and prevention of chronic diseases. Evid Based Complement Alternat Med 2005;2;513–20.
41. Tagawa N, Hidaka Y, Takano T, Shimaoka Y, Kobayashi Y, Amino N. Serum concentration of androstenediol and androstenediol

sulfate, and their relation to cytokine production during and after normal pregnancy. Steroids 2004;69:675–80.
42. Boye KR. Physiologischer Einfluss adrenaler Androgene und Glucocorticoide auf den Unterarmknochen im Wachstumsalter bei gesunden Kindern. Dissertation. FU Berlin. Available at http://www.diss.fu-berlin.de/2006/4/.
43. Imin N, Nizamidin M, Wu T, Rolfe BG. Factors involved in root formation in Medicago truncatula. J Exp Bot 2007;58:439–51.