Acta Scientific NUTRITIONAL HEALTH (ISSN:2582-1423)

Volume 5 Issue 12 December 2021

Research Article

Aspergillus oryzae Fermented Brown Rice and Bran Supplement "FBRA" for Health and Cancer Prevention

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Received: October 19, 2021

Published: November 12, 2021

Abstract

Relationship between brown rice eating and health has been well recognized, but it is an empirical basis without solid scientific shreds of evidence. Fermented brown rice and bran with *Aspergillus oryzae* (FBRA) were developed almost 50 years ago to supplement white rice eating. We found spontaneous cancer remission among the FBRA users, so we resurvey the GENKI study cohort (Genmai Epidemiology, Nutrition, and Kenko Innovation; n = 1200) and found 180 FBRA users.

We compared the effect of FBRA on bowel movement by brown rice and white rice eaters. One hundred eleven volunteers among the GENKI study provided their feces for intestinal microbiota analysis, so it became possible whether or not white rice eaters with FBRA intake showed a similar profile to brown rice eaters. FBRA users showed good bowel condition as well as brown rice eaters. Brown rice eaters with FIBRA enhanced the profile proportion of *Faecalibacterium prausnitzi* (6.2 to 8.9%), *Blautia wexlerae* (2.0 to 3.1%), *Ruminococcus bromii* (1.1 to 2.1%), and *Bacteroides uniformis* (0.9 to 3.3%). The principal component analysis showed a different pattern in the genmai and FBRA group.

Long FBRA users by a separate questionnaire survey showed a low cancer incidence ($p = 0.05$), diabetes mellitus, dyslipidemia, and hypertension ($p < 0.0001$). Dietary fiber, γ-oryzanol, high vitamin and minerals, antioxidant activity, and various metabolites may contribute to multiple effects on health and disease prevention. The present paper provides information on new foodstuffs for cancer prevention.

Introduction

World Health Organization survey estimated the number of cancers worldwide in 2018 to be about 18.1 million, and the number of cancer-related deaths was at 9.6 million [1]. Although the five year-survival has been improved, the death rate of intractable cancers is still high [2]. IARC has made a long list of risk factors of cancers, but preventive interventions are still limited [3]. One-third of cancers could be prevented by diet, physical activity, and non-smoking [4,5]. The American Cancer Institute has reviewed a vast body of literature and scrutinized research reports on diet and cancer [6]. In the United States, functional foods from the perspective of cancer-preventing Designer's Foods have been proposed by National Cancer Institute [7]. After that, with a concrete image, it was taken over by the 5-A-Day movement, which was about how much to eat [8].

Besides, the development of treatment for cancer survivors after relapse and metastasis has been a lengthy endeavor. Watanabe compiled series of double primary cancers and cancers with spontaneous regression when he worked in the National Cancer Center in Japan [9]. He reported the case of a woman with breast cancer, 3.5 cm in diameter with lymph node metastasis, who relapsed two years later after complete resection. The patient refused chemotherapy and tried FBRA (Fermented Brown rice and Rice bran with

Aspergillus oryzae: Genmai-Koso). Three years of daily intake of FBRA improved her condition, and she seemed to be cured. Several other patients also showed the effect of FBRA [10].

FBRA was made by Teruaki Iwasaki and Etsuji Okada in 1971 [11]. FBRA was conceived after the children of Iwasaki, 1 and 3 years old, discontinued eating brown rice because of its hardness. Dr. Etsuji Okada later added a method of fermentation of genmai with *Aspergillus* to produce fully processed FBRA. After three months of a trial of Iwasaki's family, all resulted in the recovery of health. In October 1971, Drs. Okada and Iwasaki began the industrial-scale production of FBRA. Since then, FBRA has had a sales duration record of 50 years. FBRA was registered as a food supplement manufactured by fermenting a mixture of brown rice and rice bran with *Aspergillus oryzae* to improve its digestibility [11].

Aspergillus oryzae contains several types of enzymes that metabolize carbohydrates, protein, and lipid. It produces a variety of active substances during fermentation. Brown rice, also known as *Kobei*, was a critical constituent of traditional Kampo medicine [12]. Its pharmacological properties include the fortifying of *qi* and the spleen through nourishing effects and anti-inflammatory effects. The active components of *Kobei* are vitamins (E, B_1, B_2), starch, dextrin, and γ-oryzanol [13].

Sagen Ishizuka [14] and Kenzo Futaki proposed genmai (brown rice) diet in combination with wellness fasting 100 years ago [15]. So, it is essential to make evidence-based data on genmai eating people in terms of disease prevention [16]. Japanese cuisine has become one of the world's legacies by beautiful arrangement and fantastic taste, but the medical evaluation of brown rice was left behind. It is necessary to investigate the status by well-designed epidemiological studies. GENKI [abbreviation of "Genmai Epidemiology Nutrition and Kenko (health) Innovation] study was conceived to find a solution by accumulating integrated evidence for healthy longevity [17]. We made the Public Health Center (JPHC) cohort study with more than 140,000 residents in 11 different local districts in Japan. We did not differentiate polished white rice and brown rice in the rice category, so we had to start a new cohort study to clarify the effect of brown rice [18].

Japanese people prefer to consume white rice, and particular groups like macrobiotic eat brown rice. Our previous GENKI study strongly suggested that brown rice intake improved health conditions by preventing obesity compared with white rice [16]. This study examined the disease preventive effects of genmai and supplemental FBRA on health, mainly focusing on cancer and non-communicable diseases. Bowel movements and microbiota profile composition were good markers of health effects.

Methods

Reconstructed database from GENKI study

The GENKI Study was conducted to find lifestyle-related factors, primarily focusing on dietary life [16]. Habitual brown rice eaters were only a few, so we had to find a particular group like macrobiotics. Eight groups joined our study. We had asked about a current health condition, bowel movement with stool feature, history, health condition changes from the last year, alcohol consumption, tobacco, education, and income. Drugs and supplements intake by groups provided information about group characteristics.

Resurvey of the GENKI 1 database found that 180 participants used FBRA to supplement 1223 participants, so we extracted these cases for the present study [DB1] (Figure 1).

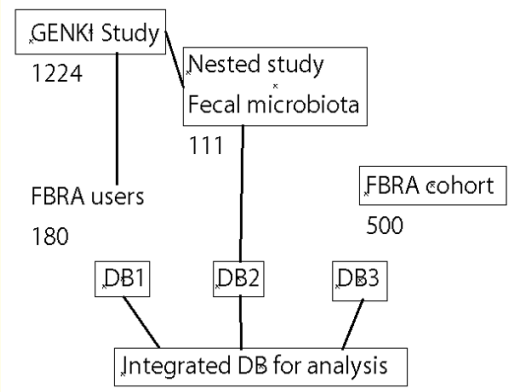

Figure 1: Structure of the study.

We did the examination of intestinal microbiota in 111 volunteers among 1224 participants in GENKI study participants [DB2]. Technosuruga Laboratory analyzed fecal microbiota. The Metagenome@KIN software (World Fusion Co., Ltd., Tokyo) and the Techno-Suruga Lab Microbial Identification Database DB-BA10.0 (Techno-Suruga Laboratory) were used for homology research. Our study found that brown rice eaters had ideal body weight associated with good bowel movement, suggesting a good intestinal environment. The excellent composition of microbiota in genmai eaters seemed to contribute to their health [19,20].

Questionnaire survey of FBRA users

We want to know about the long-term effects of FBRA consumption. We recruited about 500 collaborators through the dealers of Genmai-Koso Co. Ltd. Questionnaire survey of FBRA users was carried out on online sales registers. The district manager explained the purpose of the study, collected each datum after getting informed consent.

The simple questionnaire included name, gender, date of birth, living area, history of diseases, current account, quantity, and kinds of FBRA taken per day, duration of usage, etc. Data were collected during four years, from 2016 to 2019 [DB3].

Nutrients and functional factors in FBRA

Nutrients and functional factors in FBRA were measured every year at the Japan Food Analysis Center [21]. Annual scientific group meeting provided up-to-date experimental and biochemical data about FBRA. The value was compared with our previous data of cooked genmai rice [22,23].

Ethical issues

Genmai users generally join special wellness-oriented groups, so we called to participate in the GENKI study through the Japan Macrobiotic Association [24-27]. The Ethics Review Board Committee of the Life Science Promoting Association reviewed and approved the research plan (No. 003 in September 2015). Permission of follow-up and sub-analysis was included in the study plan. The Genki Study Office gathered written informed consent.

For summation and data publishing of the questionnaire from FBRA users were done in the Genmai Koso Co. Ltd. Participants to the questionnaire survey voluntarily joined after explaining the purpose of the study. Written informed consent was taken at the time of the first mail survey. The Ethics Review Board of the Life Science Promoting Association approved the mid-term analysis (No. 002 in August 2021).

Statistical analysis

We extracted the FBRA users from the GENKI database for analysis [DB1]. Other DataBase [DB2, DB3] obtained from the questionnaires were compiled on an Excel database and transferred to an SPSS database (Figure 1). The SPSS statistical package ver.24 was used [28]. Non-parametric analysis and parametric analysis were used for categorical data and continuous variables, respectively. The significance level of the decision was shown by $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. In the case of microbiota profile species, we selected more than 1% in the median or 75th percentile.

We downloaded the incidence and mortality rate of diseases to calculate the expected number of diseased patients from the Information Center of the National Cancer Research Center and the Ministry of Health, Labour and Welfare [29,30].

Results

Demographic data and rice category

The participant group showed female dominancy in middle age and different consumption of rice (Table 1).

The brown rice consumption was high in the Sogo-Igaku, Seishoku, CI, and Keio group, derived from Integrated Medicine or Macrobiotics [14,15]. The other four groups showed around 30% or less than 20%.

White rice eaters were 390 (33.5%) subjects, mixed-white and brown rice in 172 (14.8%), and brown rice in 601 (51.7%) (Table 1). Brown rice was eaten in two mixtures (92; 52.9%) and in three combinations (24; 96%), but these cases were deleted for further analysis.

Among all participants (Males = 365, Females = 809), current consumers of brown rice had a significantly lower BMI among all categories (BMI of brown rice eaters = 20.6 ± 2.0, and that of white rice eaters= 22.3 ± 3.3; $p < 0.000$). Brown rice eaters preferred to eat flexitarian style, taking vegetables and fish, avoiding meat, dairy products, and western fatty foods. The oily and spicy taste was also avoided, and they preferred fresh, organic, no additives, without genetically modified foodstuff, and locally produced.

Supplement intake

Supplement intake was less than 10% of the population, except for FBRA, vitamin C, and calcium. FBRA was highly consumed in Genmai-Koso and Sogo-Igaku (Integrated Medicine) group (Table 2). Multi-vitamin, multi-mineral, vitamin B complex, vitamin E, iron, DHA/EPA, nutrient drink, lactobacillus, ginkgo leaves, and others were significantly less consumed in the body of genmai eaters. Fermented mixed vegetable juice "enzyme drink (Koso)" was highly consumed in the KEIO group and dietary fiber in the Miki group (Table 2).

		N		Age		Rice Consumption category					
Group	**Category**	**Male**	**Female**	**Mean age**	**Sd**	**White rice**		**Mix rice**		**Brown rice**	
Sogo-igaku	Integrated med	73	144	62.8	15.3	37	17.3%	39	18.2%	138	64.5%
Seishoku	Macrobiotics	38	154	53.9	14.6	11	5.8%	23	12.0%	157	82.2%
CI	Macrobiotics	35	71	55.4	16.4	6	5.7%	11	10.4%	89	84.0%
Keio	Macrobiotics	16	63	41.2	14.3	14	18.2%	3	3.9%	60	77.9%
Genmai-koso	Wellness	88	86	47.3	15.3	86	49.4%	31	17.8%	57	32.8%
Mie prefecture	Wellness	50	102	51.1	16.4	103	70.5%	20	13.7%	23	15.8%
Miki	Wellness	13	65	55.3	14.2	50	64.1%	14	17.9%	14	17.9%
Zen fasting	Zen fasting	52	124	51.8	13.3	83	46.9%	31	17.5%	63	35.6%
Total		365	809	53.3	16	390	33.5%	172	14.8%	601	51.7%

Table 1: Demographic data of GENKI Study participants by their group.

		Groups									
Supplement		**Sogo-igaku**	**Seishoku**	**CI**	**Keio**	**Genmai-koso**	**Mie**	**Miki**	**Zen fasting**	**Total**	**p**
Supplement, NOS	n	114	52	41	40	129	48	69	77	570	0.000
	%	55.9%	28.7%	42.7%	57.1%	77.2%	34.5%	93.2%	46.7%	52.0%	
Multivitamin	n	20	5	6	6	8	13	13	16	87	
	%	9.2%	2.6%	5.7%	7.6%	4.6%	8.6%	16.7%	9.0%	7.4%	0.004
Minerals	n	10	8	7	11	6	6	16	17	81	
	%	4.6%	4.2%	6.6%	13.9%	3.4%	3.9%	20.5%	9.6%	6.9%	0.000
Vitamin Bs	n	18	7	7	5	12	6	26	19	100	
	%	8.3%	3.6%	6.6%	6.3%	6.9%	3.9%	33.3%	10.7%	8.5%	0.000
Vitamin C	n	24	12	6	8	32	11	39	31	163	
	%	11.1%	6.3%	5.7%	10.1%	18.4%	7.2%	50.0%	17.5%	13.9%	0.000
Vitamin E	n	13	6	0	4	5	7	33	18	86	
	%	6.0%	3.1%	0.0%	5.1%	2.9%	4.6%	42.3%	10.2%	7.3%	0.000
Fe	n	7	9	3	13	9	7	22	19	89	
	%	3.2%	4.7%	2.8%	16.5%	5.2%	4.6%	28.2%	10.7%	7.6%	0.000
Ca	n	21	8	3	10	9	6	32	21	110	
	%	9.7%	4.2%	2.8%	12.7%	5.2%	3.9%	41.0%	11.9%	9.4%	0.000
DHA/EPA	n	13	9	2	7	4	4	9	12	60	
	%	6.0%	4.7%	1.9%	8.9%	2.3%	2.6%	11.5%	6.8%	5.1%	0.015
Nutritional Drink	n	7	2	2	4	4	4	2	2	27	
	%	3.2%	1.0%	1.9%	5.1%	2.3%	2.6%	2.6%	1.1%	2.3%	0.525
Enzymes	n	10	11	2	15	5	7	1	5	56	
	%	4.6%	5.7%	1.9%	19.0%	2.9%	4.6%	1.3%	2.8%	4.8%	0.000

FBRA	n	33	11	8	1	114	2	9	3	181	
	%	15.2%	5.7%	7.5%	1.3%	65.5%	1.3%	11.5%	1.7%	15.4%	0.000
Dietary fiber	n	7	5	5	2	15	6	37	24	101	
	%	3.2%	2.6%	4.7%	2.5%	8.6%	3.9%	47.4%	13.6%	8.6%	0.000
Oligosaccharide	n	6	3	3	0	9	1	12	8	42	
	%	2.8%	1.6%	2.8%	0.0%	5.2%	0.7%	15.4%	4.5%	3.6%	0.000
Chondroitin sulfate	n	4	1	1	0	2	2	2	1	13	
	%	1.8%	0.5%	0.9%	0.0%	1.1%	1.3%	2.6%	0.6%	1.1%	0.704
Peptid	n	8	6	2	0	3	4	11	7	41	
	%	3.7%	3.1%	1.9%	0.0%	1.7%	2.6%	14.1%	4.0%	3.5%	0.000
Lactobacillus	n	23	14	5	0	18	7	12	15	94	
	%	10.6%	7.3%	4.7%	0.0%	10.3%	4.6%	15.4%	8.5%	8.0%	0.005
Others	n	50	31	18	10	41	14	29	22	215	
	%	23.0%	16.1%	17.0%	12.7%	23.6%	9.2%	37.2%	12.4%	18.3%	0.000

Table 2: Supplement consumption by each participated group.

FBRA was a substitutive supplement to genmai, so it was employed by white rice eaters, especially in the Genmai-Koso group.

Bowel condition

Brown rice eaters had bowel movements once or twice a day, and their stools showed the shape of a banana. Dietary habits contribute to their healthy feeling in conjunction with other lifestyles.

Nearly 60% of men and 48-55% of women had a once-a-day bowel movement. In more than half, brown rice without FBRA and white rice with FBRA induced daily bowel movement. An increased number of bowel movements was present in the genmai + FBRA group.

"Less than 3/week" presented in 21.4% white rice group, while it decreased to 5.4% in FBRA added group. The analysis by rice categories clearly showed a benefit among brown rice eaters (Table 3). White rice eaters taking FBRA changed their bowel movement toward brown rice eaters. Daily and 2/day movement among white rice eaters was about 46%, while it increased to 78.4% by FBRA addition.

Banana shape stool was most frequently present in the brown rice eaters. FBRA taking moved toward hard feces. The diarrhea stool, or "alternative watery and solid," was high in white rice without FBRA.

Bowel movement	White rice		Brown rice	
	FBRA -	FBRA +	FBRA -	FBRA +
N	27	37	18	20
1/week	0	2	0	1
	0%	2.70%	0%	2.50%
2/week	2	2	1	0
	7.10%	2.70%	5%	0%
3/week	4	0	0	3
	14.30%	0%	0%	7.50%
4/week	7	5	2	3
	25%	6.80%	11.10%	7.50%
Daily	11	40	9	17
	39.30%	54.10%	50%	42.50%
2/day	2	18	6	13
	7.10%	24.30%	33.30%	32.50%
3/day	2	7	0	3
	7.10%	9.50%	0%	7.50%
Feature				P = 0.032
Diarrhea	1	0	2	2
	3.60%	0%	2.70%	5%

Soft	0	2	0	2
	0%	11.10%	0%	5%
Banana	5	3	27	8
	17.90%	16.70%	36.50%	20%
Hard	14	12	36	24
	50%	66.70%	48.60%	60%
Diarrhea/	6	1	9	4
Solid	21.40%	5.60%	12.20%	10%
				P = 0.021

Table 3: Bowel movement and stool figures by rice and FBRA combination group.

Microbiota

One hundred nine healthy subjects (18 males, 90 females, unknown 1) provided stools for analysis in the GENKI study.

Common bacterial profiles of white rice eaters at phylum level were *Firmicutes* 44.6 ± 10.7%, *Bacteroides* 19.1 ± 7.5%, *Actinobacteria* 7.6 ± 6.7%, *Proteobacteria* 0.6 ± 0.4% and *Verrucomicrobia* 6.4 ± 13.7% (max 39.4%). Brown rice eaters also showed dominancy of *Firmicutes*, but higher *Proteobacteria* and lower *Verrucommicrobia*.

At the species level, the combination of rice and the usage of FBRA did not show a remarkable difference (Table 4). *Faecalibacterium prausnitzi* was the top (median: 6.7-8.9%), then *Blautia wexlerae* (2.1-3.8%), *Fusicatenibacter saccharivorans* (1.6-2.6%), *Bacteroides vulgatus* (0.9-1.8%), *Bifidobacterium adolescents* (0.03-2.7%), *Bacteroides uniformis* (0.9-3.3%), etc. followed. The principal component analysis, Group 1 (white rice) and Group 2 (white rice +FBRA) showed the same pattern, but Group 3 (genmai) and Group 4 (genmai+FBRA) showed different components. With the addition of FBRA, variability in *Bacteroides, Bifidobacteria*, and *Prevotela copri* increased although no statistical significance (Figure 2).

Brown rice+FBRA users showed low *Prevotella copri, Akkermansia muciniphera, Streptococcus salivarius, Megamonas funiformis*, and *Bacteroides stercoris.* In the case of *Bifidobacterium longus*, FBRA users did not show a high prevalence.

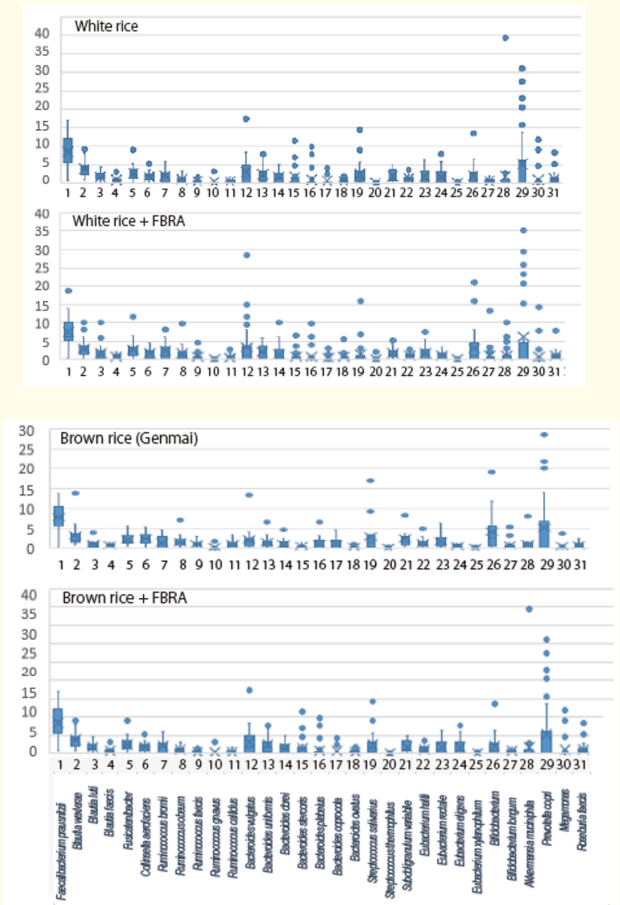

Figure 2: Intestinal microbiota profile composition by rice and FBRA.

The high prevalence of *Faecalibacterium prausnitzii* (7-8%) suggested a benefit of butyrate production, and *Blautia wexlerae* (3-4%) indicated the control on intestinal immunity [19,31-33].

The addition of FBRA increased the diversity and movement of *Bacteroides, Ruminococcus, Blautia, Bifidobacteria* was recognized. Increased *Prevotela copri* was presented in FBRA added person (Figure 1).

Users of FBRA

The distribution of FBRA users by sex and age category was shown in table 7. Average age and sd were 65.8 ± 16.6 (n = 189) in males and 68.4 ± 15.6 (n = 307) in females (Table 5). The dose and duration of FBRA usage was 9.5 ± 5.9 packs/day, and duration of

	White rice n = 27			White rice + FBRA n = 37			Brown rice n = 18			Brown rice + FBRA n = 20		
	Median	**25**	**75**	**Median**	**25**	**75**	**Median**	**25**	**75**	**Median**	**25**	**75**
Fecalibacterium prausnitzii	8.942	5.546	12.036	6.211	5.333	10.203	7.788	5.676	10.343	6.747	5.836	11.535
Blautia wexlerae	3.783	2.347	4.716	2.269	1.484	3.756	2.078	1.579	3.695	3.111	2.364	4.625
Blautia luti	1.498	1.028	2.643	0.991	0.403	2.440	0.837	0.322	1.416	1.830*	0.643	3.102
Blautia faecis	0.828	0.515	1.134	0.619	0.365	1.248	0.829	0.498	1.152	0.905	0.628	1.407
Fusicatenibacter saccharivorans	2.374	1.415	3.693	2.302	0.914	3.245	1.610	1.184	3.231	2.629	1.298	3.855
Collinsella aerofaciens	1.901	0.953	2.374	1.969	0.263	2.471	2.413	1.162	3.340	1.483	0.007	2.808
Ruminococcus bromii	1.840	0.014	2.771	1.124	0.007	3.155	1.075	0.000	3.015	2.102	0.015	3.416
Ruminococcus obeum	0.972	0.318	1.601	0.961	0.347	2.185	0.907	0.716	2.222	0.751*	0.222	1.170
Ruminococcus faecis	0.396	0.241	0.660	0.335	0.119	0.708	0.817	0.457	1.569	0.549	0.023	0.878
Ruminococcus gnavus	0.023	0.008	0.136	0.005	0.000	0.063	0.003	0.000	0.046	0.048	0.001	0.442
Ruminococcus callidus	0.020	0.000	0.857	0.045	0.000	1.031	0.771	0.141	1.611	0.006	0.000	0.408
Bacteroides vulgatus	1.828	0.009	5.042	1.163	0.028	3.530	1.484	0.437	2.578	0.896	0.015	6.984
Bacteroides uniformis	1.730	0.477	3.290	1.936	0.548	3.649	0.922	0.540	1.772	3.321	0.659	4.869
Bacteroides dorei	1.341	0.018	2.610	0.309	0.003	2.555	0.330	0.024	1.674	0.125	0.006	4.034
Bacteroides stercoris	0.122	0.000	1.823	0.008*	0.000	0.671	0.079	0.002	0.674	0.000	0.000	0.061
Bacteroides plebeius	0.003	0.000	0.345	0.002	0.000	0.028	0.000	0.000	2.023	0.001	0.000	0.008
Bacteroides coprocola	0.000	0.000	0.235	0.000	0.000	0.015	0.093	0.000	1.908	0.000	0.000	0.058
Bacteroides ovatus	0.358	0.019	0.703	0.170	0.067	0.644	0.199	0.096	0.301	0.821*	0.104	1.911
Streptococcus salivarius	1.458	0.514	3.384	0.403	0.118	1.108	1.501	0.313	3.230	0.787*	0.136	1.634
Streptococcus thermophilus	0.003	0.000	0.006	0.000	0.000	0.012	0.001	0.000	0.008	0.000	0.000	0.005
Subdoligranulum variabile	1.287	0.686	3.638	1.339	0.761	2.498	1.803	0.879	2.882	2.228	0.880	4.362
Eubacterium hallii	1.279	0.603	1.668	0.952	0.678	1.505	0.992	0.650	1.679	1.168	0.443	1.622
Eubacterium rectale	0.894	0.163	3.360	1.308	0.211	2.648	0.997	0.505	2.846	0.475	0.024	2.821
Eubacterium eligens	0.847	0.220	3.089	0.695*	0.171	1.709	0.424	0.129	0.923	0.295	0.000	0.743

Eubacterium xylanophilum	0.000	0.000	0.129	0.015	0.000	0.086	0.025	0.000	0.115	0.000	0.000	0.026
Bifidobacterium adolescentis	0.858	0.008	2.923	1.142	0.028	4.494	2.698	0.565	5.663	0.034	0.003	3.843
Bifidobacterium longum	0.473	0.106	1.040	0.453	0.122	0.868	0.160	0.032	0.794	0.223	0.001	1.102
Akkermansia muciniphila	0.053	0.000	1.034	0.057	0.002	1.116	0.137	0.000	1.627	0.005*	0.000	0.026
Prevotella copri	0.008	0.002	6.068	0.009	0.003	4.632	0.006	0.000	6.757	0.008	0.001	0.042

Table 4: Microbiota profile at the species level by a combination of rice and FBRA.

Age_cat	Sex		Total
	M	F	
10	0	5	5
20	6	4	10
30	8	10	18
40	14	24	38
50	23	42	65
60	27	57	84
70	68	95	163
80	38	56	94
90	5	13	18
100	1	0	1
Total	190	306	496

Table 5: Age and sex category of FBRA users.

use was 21 ± 9.1 years in males, and 10.5 ± 6.3 packs/day and 20.6 ± 9.0 years in females.

There was a hypothesis explaining that this population may be less affected by cancers. Cancer incidences were collected from 2016 to 2019. History of cancer at the baseline was 40 (brain tumor 1, head and neck region 4, gastric cancer 2, pancreas cancer 1, colon cancer 5, renal cancer 2, bladder cancer, prostatic cancer 1, lung 1, breast cancer 15, uterine cancer 2, ovarian cancer 4). The incidence of cancer in 2016 was three (colon, rectum, ovary), four (appendix 2, colon, breast, pancreas) in 2017, five (esophagus, colon, pancreas, bladder, prostate, breast) in 2018, and seven (stomach 2, pancreas 2, cecum, bladder, breast) in 2019. The total number of cases during four years was 21. (O; 3+5+6+7 = 21) and the expected number was 31 (E; 7.75*4 = 31). So, the O/E ratio was 0.7, which was a significantly low incidence (Table 6). Site-specific analysis showed low stomach cancer and high pancreas cancer. It may need further careful follow-up in these cases. In colorectum and breast cancers, the O/E ratio was nearly one.

Site	O	E	O/E	c2	p
All site	21	31	0.7	3.23	0.05*
Stomach	2	4.24	0.5	1.18	0.281
Colorectum	5	4.88	1	0.00	0.957
Pancreas	4	1.52	2.6	4.05	0.044*
Breast	3	2.56	1.2	0.08	0.783

Table 6: Site-specific cancer cases and the expected number.

All site O/E ratio was significantly low by poison test P (#<=21|31) <0.05.

In diabetes mellitus, dyslipidemia and hypertension observed number was 23, 18.5, and 56, respectively, and these values showed a highly significant difference compared to the national incidence data [30] (Table 7). The above results were reflected in the small number of people, and although there was a shortage of power in four years, it seems that verification was possible.

Nutrients and functional factors in FBRA

FBRA was a mixture of brown rice (Oryzae Fructus) and rice bran fermentation by *Aspergillus oryzae*. The potentially active components were dietary fiber, vitamins (E, B_1, B_2), minerals, and γ-oryzanol (Table 8) [31]. Many other metabolites like hydroxycinnamic acids and hydroxybenzoic acid were also present [32]. The presence of amylase, acid protease, neutral protease, and lipase helped digestion. The presence of antioxidant activity (superoxide elimination capacity) could decrease free radicals inside the body.

	Prevalence		Number of cases				
	FBRA user	Nation	Observed	Expected	O/E	c2	p
Diabetes mellitus	4.60%	12.70%	23	63.5	0.36	25.83	<0.0001
Dyslipidemia	3.70%	22%	18.5	110	0.17	76.11	<0.0001
Hypertension	11.20%	48%	56	240	0.23	141.07	<0.0001

Table 7: Comparison of incidence of diabetes, dyslipidemia, and hypertension between FBRA users and nation.

	FBRA	Boiled brown rice
Energy (kcal)	406	407.5
Protein (g)	16.3	2.2
Lipid (g)	22.1	3.2
Carbohydrate (g)	47.3	95.4
Sugar (g)	23.4	92.9
Dietary fiber (g)	23.9	2.5
Na (mg)	15.2	4.2
NaCleq (g)	0.04	0.007
Ash (g)	11.7	0.2
Ca (mg)	429	10
P (mg)	2660	192.1
Fe (mg)	7.2	0.7
K (mg)	2090	142.5
Mg (mg)	1070	79.3
Mn (mg)	23.3	1.4
Zn (mg)	5.4	1.3
Cu (mg)	0.7	0.2
Se (ug)	9	nd
Vit A (IU)	-	-
Vit B1 (mg)	2.1	0.28
Vit B2 (mg)	0.8	nd
Vit B6 (mg)	3.8	nd
Niacin (mg)	66	nd
Panthotenic acid (mg)	6.9	nd
Folic acid (mg)	190	21.6
Vit B12 (ug)	0.03	nd
Biotin (ug)	48.6	nd
Vit E (mg)	9.4	1.1
Vit K1 (ug)	28	nd
Superoxide elimination capacity	1000 U/g	1278 uMTEQ
Phytin acid (g)	7.6	nd
GABA (mg)	7	10
Amylase	1600 U	nd
Acid protease	290 U	nd
Neutral protease	340 U	nd
Alkali protease	70 U	nd
Lipase	680 U	nd
	/100g water adjusted	

Table 8: Comparison of nutrients between FBRA and cooked brown rice.

Compared to the water-adjusted ordinary brown rice, protein, lipid, dietary fiber, ash, and minerals were nearly ten times high (Table 8). The presence of amylase, acid protease, neutral protease, alkali protease, and lipase works well as a digestive system. If we took FBRA at 20g, we could take vitamin E, vitamin B_6, Mg, and Fe more than that required by Dietary Reference Intake (Figure 3).

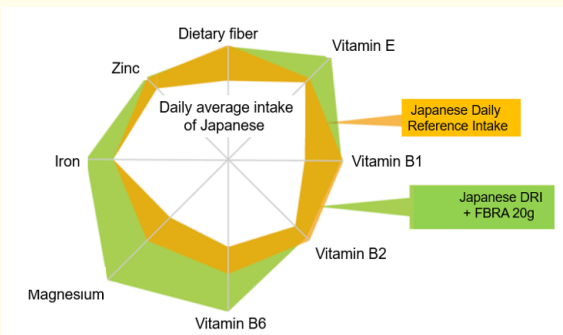

Figure 3: Rader chart showing vitamin- and mineral intake by adding 20 g FBRA to the everyday diet.

Discussion

Brown rice and bran as a functional foodstuff

Brown rice has been used as one of the constituents of traditional Kampo medicine known as 'Kobei. Fortifying qi and the spleen and have anti-inflammatory effects were present. The potential active components for the pharmacological activity of Kobei are vitamin E, B_1, and B_2, starch, dextrin, and γ-oryzanol. Recently γ-oryzanol in rice has been a focus of studies [33].

Numerous animal models varyingly demonstrated that gut microbiota could modulate host health, and brown rice eaters consistently showed good composition with butyrate-producing bacteria [34-40].

Group specificity

We found that the genmai consumption rate was quite different by people in each health-oriented group. Brown rice eater was beneficial to keep good bowel movement in conjunction with plant-based Japanese foods, avoiding meat and dairy products associated [16,17,23]. FBRA consumption was highest among the Genmai-Koso group, in which many white rice eaters used FBRA instead.

Dietary fiber of brown rice, g-oryzanol, and other functional ingredients was known to influence bowel movement and arrange intestinal environment by maintaining bacterial flora [19,36]. From the recent intestinal bacterial research, people who ingested dietary fiber have reported many bacteria producing citric acid, propionic acid, and butyric acid [38-40]. In rat experiments, FBRA caused an increase of *Bifidobacterium longum* [31,41], but in humans, *Bifidobacterium adolescentis* increased. FBRA seemed to stabilize *Prevotella copri.*

FBRA contains ten times more functional ingredients than brown rice so that various effects would fortify physiological functions and the function of ordinary nutrients. Active components like γ-oryzanol and GABA could control diabetes mellitus [42].

FBRA users

FBRA users showed a significantly low O/E ratio in diabetes mellitus, dyslipidemia, and hypertension. In the case of cancer, overall cancer incidence was significantly low compared to the public. The site-specific analysis showed variety. Rice germ and bran contain oily components such as ferulic acid and tocopherol and water-soluble components such as phytic acid and dietary fibers.

FBRA suppressed experimental carcinogenesis in many organs [43-58]. The mechanism of the carcinogenic preventive action of FBRA is unknown, but it must be the summation effect of several factors. One is the possibility of enhancing the active ingredient by the process of fermentation. FBRA has been shown to have antioxidant properties [59]. In almost all experiments in which FBRA carcinogenesis was prevented by suppression of cell proliferation in target organs. FBRA also suppressed inflammation and excessive cell proliferation caused by inflammation [60].

Many people have been abandoned by doctors and have survived under the treatment of complementary and alternative medicine. These pieces of evidence suggested that rice constituents like rice germ, rice bran, ferulic acid, and rice-related agents like FBRA are promising for the prevention of human cancers.

The weakness of our study was the data being an observational study. However, it needed a long time to clarify the relationship between dietary habits and health. The intestinal microbiota proportion could be the biomarker of health effects. In this sense, integrated research is more required in human epidemiology.

Conclusion

The relationship between brown rice eating and health has been well recognized, but it is an empirical basis without solid scientific evidence. Fermented brown rice and bran with *Aspergillus oryzae* (FBRA) were developed almost 50 years ago to supplement white rice eating. We resurveyed the GENKI study cohort (Genmai Epidemiology, Nutrition, and Kenko Innovation; n = 1200) and found 180 FBRA users [DB1].

We compared the effect of FBRA on bowel movement by brown rice and white rice eaters. One hundred eleven volunteers among the GENKI study provided their feces for intestinal microbiota analysis, so it became possible whether or not white rice eaters with FBRA intake showed a similar profile to brown rice eaters [DB2]. FBRA users showed good vowel condition as well as brown rice eaters. The addition of FBRA to both white rice and brown rice eaters caused changes in intestinal microbiota profile proportion. Brown rice eaters with FIBRA enhanced the profile of *Blautia wexlerae* (2.0 to 3.1%), *Ruminococcus bromii* (1.1 to 2.1%), and *Bacteroides uniformis* (0.9 to 3.3%). *Bifidobacterium adolescentis* decreased from 2.7 to 0.03%.

Long FBRA users showed a low cancer incidence ($p = 0.05$), diabetes mellitus, dyslipidemia, and hypertension ($p < 0.0001$) [DB3]. Dietary fiber, g-oryzanol, high vitamin and minerals, antioxidant activity, and various metabolites may contribute to multiple effects on health and disease prevention. The present paper provides information on new foodstuffs for cancer and disease prevention.

Author Contributions

Conceptualization, S.W.; methodology, S.W. and K.K.; validation, K.K., and T.M.; formal analysis, S.M.; investigation, S.W.; resources, K.K., S.M., and T.M.; data curation, K.K., S.M., T.M.; writing—original draft preparation, S.W.; writing—review and editing, S.W.; visualization, S.W.; project administration, S.W.; funding acquisition, S.W. All authors have read and agreed to the published version of the manuscript.

Funding

A part of this research was supported by a grant from the Project of the NARO Bio-oriented Technology Research Advancement Institution (research program on development of innovative technology).

Acknowledgments

The authors thank the participants of the GENKI study and of FBRA follow-up study. Dr. Philippe Calain and Mizuki Calain contributed to the discussion and editing of the English language. We appreciate Professor Emeritus Hiroshi Kobayashi for his constructive and critical debate.

Conflicts of Interest

S.W,; K.K.; S.M. declare no conflict of interest. T.M. is an employee of Genmai-Koso Co. Ltd. The company had no role in the design of the study; in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

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