

Probiotic Survey in Cancer Patients Treated in the Outpatient Department in a Comprehensive Cancer Center

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Abstract

Purpose. Availability without prescription restriction, low cost, and simple oral administration allow cancer patients to use probiotics without knowledge of potential risks. We present a survey of probiotic use and the association with patient tumor characteristics in cancer patients treated at the outpatient department of the National Cancer Institute in Slovakia. **Patients and Methods.** Between March and December 2014, 499 patients were asked to evaluate their overall experience with probiotics by questionnaire form, including the length and method of use relative to anticancer therapy, expectations, side-effect experiences, understanding of the possible risks, dietary supplement use, and others. The relevant data were statistically evaluated. **Results.** The cohort consisted of 323 women (64.7%) and 176 men (35.3%); 91.6% were undergoing chemotherapy (2.6% together with radiotherapy) and 8.4% had no anticancer therapy. The prevalence of probiotic use was 28.5% and only 12 patients using probiotics (8.5%) described negative side effects. Most patients declared consideration of probiotic use based on recommendation from a physician (37.3%) or a pharmacist (14.8%). Nevertheless, up to 86.6% of patients declared no knowledge of possible risks. Statistically significant correlation was found between probiotic use and age of patients ($P < .008$), gender ($P < .023$), and taking other dietary supplements ($P < .000002$). **Conclusions.** In this prospective study, we present for the first time the prevalence, side-effect experience, and aspects that most likely influence probiotic use in cancer patients. Minimal knowledge of risks underlines the importance of an active approach by oncologists to inform patients about probiotic safety.

Keywords

probiotics, cancer, chemotherapy, dietary supplements, safety, immunocompromised cancer patients, oncologist to patient communication

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Introduction

Cancer patients undergoing chemotherapy or radiation therapy often experience nausea, vomiting, diarrhea, and loss of appetite, leading to a lower dietary intake and weight loss. It is estimated that more than 80% of patients suffering from cancer use vitamins, minerals, herbs, and other supplements, including probiotics during the course of their disease.¹ However, the use of dietary supplements during anticancer treatment remains controversial. The number of available commercial products for alternative and complementary medicine has been increasing. Limited evidence confirming their safety and benefits from human clinical studies has led to a recommendation for cancer patients to take only moderate doses of dietary supplements.²

Most supplements are safe and provide nutritional support not obtained in the patient's current diet to ameliorate specific pathophysiological conditions and to address the patient's needs. On the other hand, supplemental intake might change the metabolism of anticancer drugs and

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consequently affect the outcome of therapy. Moreover, besides the beneficial effects associated with probiotic administration, there could be several adverse events, including potentially life-threatening conditions such as sepsis, because of immunosuppression in cancer patients undergoing chemotherapy. As many as 50% or more of patients with cancer take vitamins, herbal preparations, and other supplements, including probiotics, without medical guidance.^{3,4} Availability without prescription restriction, low cost, and simple oral administration allow cancer patients to use probiotics without knowledge of the potential risk. Because of this fact, the safety of probiotic use in immunocompromised cancer patients has become a very important issue these days.

Probiotics are live microorganisms, which as drugs or food supplements help maintain a healthful beneficial microbial balance in the digestive tract of a human or other host.^{5,6} The human gastrointestinal tract harbors a complex community containing more than 100 trillion microbial cells, which influence human physiology, nutrition, and metabolism. Intestinal bacteria play a role in vitamin B and vitamin K synthesis, as well as metabolizing bile acids, sterols, and xenobiotics. Moreover, commensal bacteria have the potential to activate the immune system. Stimulatory signals provided by microflora together with the epithelial barrier system provides the first line of defense against pathogens.⁷ Recently, extensive research on the influence of gut microbiota on human health and disease points in the direction of intestinal flora modification in the prevention and treatment of gastrointestinal disorders.⁸ Huge progress in high-throughput sequencing technologies leading to phylogenetic assignment of 16S rRNA sequences from gut or stool samples as well as parallel recent developments in nongenomic techniques is rapidly increasing our knowledge of the resident species.^{9,10}

Multiple indications for probiotics include gastrointestinal disorders, prevention and treatment of infectious and antibiotic-induced diarrhea,¹¹ and treatment of liver insufficiency,¹² lactose intolerance,¹³ inflammatory bowel disease,¹⁴ and irritable bowel syndrome.¹⁵ The main use of probiotics in cancer care is in the treatment of intestinal toxicity during both chemotherapy and radiation. Clinical studies showed fewer episodes of high-grade diarrhea and less abdominal discomfort in cancer patients receiving probiotic strains when undergoing chemotherapy^{16,17} or abdominal and pelvic radiation.^{18,19} No adverse effects of a serious nature have been reported after probiotic consumption in generally healthy people.²⁰ However, some case reports have identified probiotic strains used in therapy to be involved with sepsis. At least 8 cases of *Lactobacillus* bacteremia²¹⁻²⁶ and 9 cases of overt sepsis associated with *Saccharomyces boulardii* (*cerevisiae*), *Lactobacillus* GG, *Bacillus subtilis*, *Bifidobacterium*

breve, or combination probiotics have been reported.²⁷⁻³³ Moreover, *S cerevisiae* fungemia has been described in immunosuppressed (19 patients [31%]) and critically ill patients (28 [46%]), indicating that probiotics should be carefully used, particularly in patients with weakened immune systems.³⁴

Currently, there is lack of data regarding the exact prevalence of probiotic use in cancer patients in the literature. Before starting probiotic use, each cancer patient should discuss the potential risks/benefits of use, according to evidence-based medicine, with the oncologist or pharmacist, taking into account current immune status. However, it is estimated that 38% to 60% of patients with cancer do not inform their doctor, pharmacist, or nurse about taking nutritional supplements.¹ An open market for probiotics is expanding worldwide despite little research on consumer characteristics. Here, we present a survey of probiotic use and the association with patient tumor characteristics in cancer patients treated at the outpatient department of the National Cancer Institute in Slovakia.

Patients and Methods

In this survey, cancer patients undergoing treatment in the outpatient department hospitalized at the National Cancer Institute between March and December 2014 were included. All patients were required to provide written informed consent before enrollment and were asked to evaluate their overall experience with probiotic use during the course of their disease. The relevant data were collected by special questionnaire filled out by a pharmacist based on individual interview with patients. Questionnaire forms included questions about probiotic brand name, the initial source of information about the possibility of probiotic use, the length and method of use relative to anticancer therapy, expectations, side-effect experiences, and any changes detected after probiotic use. The study protocol was reviewed and approved by the Ethical Committee of the National Cancer Institute of Bratislava, Slovakia.

Statistics

Patient characteristics were summarized and tabulated using the mean or median (range) for continuous variables and frequency (percentage) for categorical variables. Analyses of association between probiotic use and patients/tumor characteristics were performed using a *t*-test for continuous variables, whereas Fisher's exact test or the χ^2 test when appropriate was used for categorical variables. All reported *P* values were 2 sided. For all statistical analyses, a *P* value <.05 was considered as significant. Statistical analyses were performed using NCSS 2007 software (J Hintze, 2007, Kaysville, UT).

Table 1. Patient Characteristics.^a

Variable	n	Percentage
Number of patients	499	100
Age (years)		
Mean ± Standard error of mean	58.5 ± 0.56	
Gender		
Female	323	64.7
Male	176	35.3
Patient receiving chemotherapy (CT)	457	91.6
Patient receiving radiotherapy (RT)	13	2.6
Patient receiving CT and RT	13	2.6
Patient without current anticancer therapy	42	8.4
Gastrointestinal tract cancer	131	26.1
Lung cancer	25	5
Brain cancer	9	1.8
Breast cancer	96	19.1
Urogenital system cancer	44	8.8
Gynecological cancer	56	11.1
Leukemia	37	7.4
Lymphoma	72	14.4
Multiple myeloma	12	2.4
Others	20	4
Use of others dietary supplements	202	40.5

Abbreviations: CT, chemotherapy; RT, radiotherapy.

^aTwo patients had more than 1 type of cancer.

Results

Patient Characteristics

In total, 499 patients were included in the presented survey. The cohort of patients consisted of 323 women (64.7%) and 176 men (35.3%); 91.6% were undergoing chemotherapy (2.6% together with radiotherapy), and 8.4% had no anticancer therapy. The 3 most frequent diagnoses were gastrointestinal tumors (26.1%), breast cancer (19.1%), and lymphomas (14.4%). Two patients had more than 1 cancer diagnosis. Mean age of patients was 58.5 ± 0.56 years, and 50.7% of all patients belonged to the early old age category (60-74 years). Patient characteristics and distribution of the entire cohort according to cancer type are presented in Table 1.

Association Between Probiotic Use and Patient/Tumor Characteristics

The prevalence of probiotic use recorded in our cohort of patients was 28.5%, and all of them used probiotics in supplemental pill form. The duration of use has been divided into the following ranges: ≤1 month, 43.7%; >1 month to ≤6 months, 32.4%; >6 months to ≤12 months, 12.7%; >12 months, 9.9%. More female than male patients had used probiotics during the course of their disease (72.5% vs 27.5%; $P < .023$). Our data showed that the highest

percentage of cancer patients using probiotics (42.3%) were in a group referred to as the early old age category (60-74 years). The mean ages of probiotic-positive compared with probiotic-negative patients were 56.2 ± 1.1 years to 59.4 ± 0.6 years, respectively.

Considering the entire cancer spectrum, the highest proportion of probiotic-positive patients was detected in the group with gastrointestinal tumors (22.5%), and breast and gynecological cancer (21.1% and 15.5%, respectively). Interestingly, data about the use within individual cancer diagnoses showed that 50% of multiple myeloma patients were taking probiotics. On the other hand, the percentage of probiotic-positive brain cancer patients was only 11%. However, the brain cancer group consisted of only 9 patients.

A statistically significant correlation was found (Table 2) between probiotic use and age of patients ($P < .008$), gender ($P < .023$), and taking other dietary supplements ($P < .000002$). A correlation between cancer type and probiotic use was not observed. However, we noticed a trend close to statistical significance in the case of gynecological malignancies ($P < .061$).

Based on the brand names of used probiotics stated by patients, our results showed that there was preference for probiotic preparations consisting predominantly of *Lactobacillus* and *Bifidobacterium* strains (Table 3). Overall, *Lactobacillus* and *Bifidobacterium* species are the most commonly used probiotic bacteria characterized as live active cultures and “good bacteria” for improving digestive balance. The majority of patients considered taking probiotics on recommendation from their doctor (37.3%), relatives (23.2%), media information (17.6%), the pharmacist (14.8%), and other patients (5.6%).

Relative to anticancer therapy, 28.9% of patients used probiotics together with chemotherapy, whereas 69.7% decided to take them on other days. A beneficial effect was described by 61.3% of patients, whereas 35.2% observed no effect (3.5% did not answer). However, 12 of 142 patients (8.5%) using probiotics described negative side effects such as diarrhea (41.7%), obstipation (16.7%), allergy (8.3%), weight gain (8.3%), flatulence (8.3%), candidiasis (8.3%), and rashes (8.3%). The patients' most frequent favorable expectations of probiotic consumption were digestion and appetite improvement (16.9%), relief of pain and problems with constipation or diarrhea (25.4%), immune system support and intestinal flora restoration (17.6%), cancer treatment (4.2%), elimination of vomiting after chemotherapy (3.5%), flatulence elimination (7%), and neutralization of stomach acid (6.3%). Concerning potential risks, 13.4% of Slovak cancer patients declared knowledge of risk information. However, 86.6% of patients had no knowledge about the potential risks associated with probiotics (Table 3).

According to available data, 202 of all 499 patients (40.5%) enrolled in the survey took dietary supplements

Table 2. Association Between Probiotic Use and Patient/Tumor Characteristics.

Variable	Probiotics Negative		Probiotics Positive		P Value
	n	Percentage	n	Percentage	
Number of patients	357	71.5	142	28.5	NA
Age (years)					
Mean \pm Standard error of mean		59.4 \pm 0.6		56.2 \pm 1.1	.008
Gender					
Female	220	68.1	103	31.9	.023
Male	137	77.8	39	22.2	
Patient receiving chemotherapy (CT)					
Yes	328	71.8	129	28.2	.722
No	29	69.0	13	31.0	
Patient receiving radiotherapy (RT)					
Yes	10	76.9	3	23.1	.767
No	347	71.4	139	28.6	
Patient receiving CT and RT					
Yes	10	76.9	3	23.1	.767
No	347	71.4	139	28.6	
Patient without current anticancer therapy					
Yes	29	69.0	13	31.0	.722
No	328	71.8	129	28.2	
Gastrointestinal tract cancer					
Yes	99	75.6	32	24.4	.260
No	258	70.1	110	29.9	
Lung cancer					
Yes	15	60.0	10	40.0	.254
No	342	72.2	132	27.8	
Brain cancer					
Yes	8	88.9	1	11.1	.301
No	349	71.2	141	28.8	
Breast cancer					
Yes	66	68.8	30	31.3	.530
No	291	72.2	112	27.8	
Urogenital system cancer					
Yes	33	75.0	11	25.0	.609
No	324	71.2	131	28.8	
Gynecological cancer					
Yes	34	60.7	22	39.3	.061
No	323	72.9	120	27.1	
Leukemia					
Yes	28	75.7	9	24.3	.581
No	329	71.2	133	28.8	
Lymphoma					
Yes	53	73.6	19	26.4	.778
No	304	71.2	123	28.8	
Multiple myeloma					
Yes	6	50.0	6	50.0	.109
No	351	72.1	136	27.9	
Others					
Yes	16	80.0	4	20.0	.460
No	341	71.2	138	28.8	
Use of others dietary supplements					
Yes	121	59.9	81	40.1	.000002
No	236	79.5	61	20.5	

Abbreviations: CT, chemotherapy; RT, radiotherapy.

Table 3. Probiotic Survey Results.

Variable	n	Percentage
Cancer patients using probiotics	142	100
Probiotic strain in commercially available product		
<i>Lactobacillus</i> sp	57	40.0
<i>Lactobacillus</i> sp + <i>Bifidobacterium</i> sp	55	38.7
<i>Bacillus coagulans</i>	11	7.8
Others (<i>Enterococcus</i> sp, <i>Streptococcus</i> sp)	19	13.5
Method of use relative to anticancer therapy		
With chemotherapy	41	28.9
Use on other days than chemotherapy	99	69.7
No data available	2	1.4
Duration of probiotic use		
≤1 month	62	43.7
>1 month to ≤6 months	46	32.4
>6 months to ≤12 months	18	12.7
>12 months	14	9.9
No data available	2	1.4
Beneficial effects observed		
Yes	87	61.3
No	50	35.2
No data available	5	3.5
Expectations of personal therapeutic benefit		
Digestion and appetite improvement	24	16.9
Relief of pain and problems with constipation and diarrhea	36	25.4
Immune system support and intestinal flora restoration	25	17.6
Cancer treatment	6	4.2
Elimination of vomiting after chemotherapy	5	3.5
Elimination of flatulence	10	7.0
Neutralization of stomach acid	9	6.3
Others	27	19.0
Side-effect experiences		
Yes	12	8.5
No	130	91.5
Knowledge about the risks associated with probiotics		
Yes	19	13.4
No	123	86.6
Reason for considering probiotic use		
Recommendation from a doctor	53	37.3
Recommendation from a pharmacist	21	14.8
Media information	25	17.6
Recommendation from other patients	8	5.6
Recommendation from relatives	33	23.2
Others	2	1.4

other than probiotics. Results showed that 51% of the patients who took supplements other than probiotics used vitamin C; other frequently used items were vitamin B,

Mg²⁺, aloe vera, green barley, and oyster mushroom. In the group of patients using probiotics, other supplements were taken by 57%, whereas among non-probiotic users, 33.9% used other supplements.

Discussion

In this survey, we aimed to point out the importance of the issue of probiotic use in cancer patients. Compared with the average population, cancer patients more often use vitamins, minerals, herbs, and other supplements, including probiotics.³⁵ Patients' decision to use complementary or alternative medicine and dietary supplements, including probiotics, depends on the severity of their disease and experiences of side effects associated with the anticancer treatment they received. Supplementation may also provide a sense of control or of being actively involved in treatment. Some patients viewed probiotics as alternatives to pharmaceutical drugs and understood probiotics as a more natural, low-risk therapeutic option.³⁶ Recent experimental studies have suggested possible antitumor effects of probiotics mediated by their anti-inflammatory effects, especially in breast and colon cancer.³⁷⁻³⁹

As presented here, the prevalence of probiotic use in a cohort of 499 Slovak cancer patients undergoing chemotherapy was recorded as 28.5%. From the clinical point of view, an important finding was that 86.6% of patients declared no knowledge about the potential risks associated with probiotics. More than half of the patients reported considering probiotic intake based on recommendation either from a physician (37.3%) or from a pharmacist (14.8%). The safety of probiotic use in cancer patients has recently become a very important issue these days, and the lack of discussion between the physician and the patient raises serious questions. To ensure optimal patient care, oncologists should take into account research findings and adequately discuss all complementary approaches with their patients. An active approach accompanied by knowledgeable explanations of potential risk might help in the prevention of adverse effects, such as the development of septic conditions resulting from the reduced capability for microbial clearance in immunocompromised or critically ill patients. Several cases of *Lactobacillus* bacteremia and fungemia have so far been reported in cancer patients.^{40,41} On the other hand, our previous study did not show any safety issues regarding septicemia caused by a probiotic strain in neutropenic patients⁴²; but outside of a clinical study, there is no room for using probiotics.

More female than male patients had used probiotics during the course of their disease in this survey (72.5% vs 27.5%; $P < .023$). This is in accord with other studies showing that women, younger patients, and patients with higher socioeconomic status more often use complementary and alternative medicine.¹ Patients with gastrointestinal tumors

used probiotics in the highest percentage, confirming the observation that probiotics are mainly used alongside gastrointestinal treatment.⁴³

To address the issue of side-effect experience, only 8.5% of patients using probiotics described negative effects. More than 40% of them experienced diarrhea, but we cannot exclude the fact that its primary cause might have been anticancer treatment and not probiotic intake. Other negative effects such as allergy, weight gain, flatulence, candidiasis, obstipation, and rashes were only occasionally observed.

As we have shown, there is a high percentage of patients reaching for probiotics and other dietary supplements when undergoing chemotherapy treatment. Damage to natural protective barriers resulting from the frequent use of chemotherapy, radiation therapy, and especially antibiotics frequently leads to disruption of gut microbial balance followed by mucositis and diarrhea. Reduction of side effects associated with chemotherapy and radiation therapy represents the main interest in the use of probiotics as an adjunctive therapy to anticancer treatment. Experimental studies and some clinical studies suggest that lactic acid bacteria might also have beneficial effects on the toxicity associated with anticancer therapy.^{42,44-46}

The prevalence of intake of other dietary supplements in our cohort was 40.5%, showing that more cancer patients preferred to use vitamins or herbs than probiotics (28.5%). Our data showed that probiotic-using patients are more likely to take other dietary supplements than non-probiotic-using patients (57% vs 33.9%, respectively). The prevalence of supplement use in healthy individuals and cancer patients has grown rapidly.⁴⁷ Because supplements often contain a mixture of biologically active chemical compounds, many health risks might be associated with their use. In addition, most dietary supplements have been tested only in nonclinical studies, and there are insufficient data on the safety and efficacy from clinical trials in humans. Therefore, reliable communication between the treating physician, and patients and their families about the use of nutritional supplements and herbal products is necessary to evaluate the possible interactions prior to the surgical treatment as well as during chemotherapy and radiotherapy. The patient should be informed about the inappropriateness of using complementary products and probiotics, the use of which could lead to interaction with the conventionally used treatment or cause potentially life-threatening conditions such as sepsis because of immunosuppression.

The survey presented here aimed to map the prevalence of probiotic use in cancer patients and find any correlation with patient characteristics. However, its major limitation is the fact that data apply mostly to outpatients undergoing chemotherapy, and we cannot state the situation in patients treated only with radiation therapy. Moreover, only a limited number of cancer patients not currently undergoing

treatment were included in this survey. Probiotics are classified as dietary supplements, and their quality should be evaluated based on viability of the bacteria, bacterial types, and enteric protection of the product if it includes bacteria incapable of passage through stomach acid. The lack of information about quality and dosage of probiotic bacteria and subjective lifestyle and diet that might interact with probiotics might cause a bias in estimation of the positive/negative effects of probiotics in outpatients. However, this survey did not aim to assess the impact of probiotics taken while undergoing cancer treatment on the improvement of patients' health status. For this purpose, further studies and clinical trials need to be performed.

In conclusion, in this prospective study, we present for the first time data about the prevalence, side-effect experiences, and characteristics that most likely influence probiotic use in cancer patients. Our results have shown differences in probiotic use related to age, gender, cancer type, and decision to take other dietary supplements. According to our data, minimal knowledge of potential risk in this patient group underlined the importance of adequate communication between oncologists and patients as the key to forming a safe alliance between conventional and complementary medicine. However, the currently available literature is not well equipped to answer questions on the safety and efficacy of probiotics in cancer patients treated with chemotherapy or radiation therapy. More research and especially well-designed clinical trials would give the physicians relevant data for evidence-based medicine.

Declaration of Conflicting Interests

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