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...
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 or abdominal and pelvic radiation.\(^16\),\(^17\)\(^18\),\(^19\) 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 \textit{Lactobacillus} bacteremia\(^11\),\(^16\),\(^21\)-\(^26\) and 9 cases of overt sepsis associated with \textit{Saccharomyces boulardii} (\textit{cerevisiae}), \textit{Lactobacillus GG}, \textit{Bacillus subtilis}, \textit{Bifidobacterium breve}, or combination probiotics have been reported.\(^27\)-\(^33\) Moreover, \textit{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, the 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 \(t\)-test for continuous variables, whereas Fisher’s exact test or the \(\chi^2\) 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).
| 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.
*Two 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 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 ± Standard error of mean           | 59.4 ± 0.6 |           | 56.2 ± 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.
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, Mg\(^ {2+}\), 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 patients\(^ {42} \); 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

### Table 3. Probiotic Survey Results.

| Variable | n  | Percentage |
|----------|----|------------|
| Cancer patients using probiotics | 142 | 100 |
| Probiotic strain in commercially available product | | |
| *Lactobacillus* sp | 57 | 40.0 |
| *Lactobacillus* sp + *Bifidobacterium* sp | 55 | 38.7 |
| *Bacillus* coagulans | 11 | 7.8 |
| Others (*Enterococcus* sp, *Streptococcus* 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 |
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.

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References
1. Richardson MA, Sanders T, Palmer JL, Greisinger A, Singletary SE. Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. J Clin Oncol. 2000;18:2505-14.
2. Norman HA, Butrum RR, Feldman E, et al. The role of dietary supplements during cancer therapy. J Nutr. 2003;133: 3794S-3799S.
3. Wanchai A, Armer JM, Stewart BR. Complementary and alternative medicine use among women with breast cancer: a systematic review. Clin J Oncol Nurs. 2010;14:E45-E55.

4. Astin JA, Reilly C, Perkins C, Child WL. Breast cancer patients' perspectives on and use of complementary and alternative medicine: a study by the Susan G. Komen Breast Cancer Foundation. J Soc Integr Oncol. 2006;4:157-169.

5. Fuller R. Probiotics in man and animals. J Appl Bacteriol. 1989;66:365-378.

6. Food and Agricultural Organization of United Nations and World Health Organization. Evaluation of Health and Nutritional Properties of Probiotics in Food, Including Powder Milk With Live Lactic Acid Bacteria. Geneva, Switzerland: FAO, WHO. Expert Consultation report 2001.

7. Goto Y, Kiyono H. Epithelial barrier: an interface for the cross-communication between gut flora and immune system. Immunol Rev. 2012;245:147-163.

8. Ciernikova S, Mego M, Hainova K, Adamcikova Z, Stevurkova V, Zajac V. Modification of microflora imbalance: future directions for prevention and treatment of colorectal cancer? Neoplasma. 2015;62:345-352.

9. Kurokawa K, Itoh T, Kuwahara T, et al. Comparative metagenome established by metagenomic sequencing. Nature. 2010;464:59-65.

10. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue revealed commonly enriched gene sets in human gut microbiomes. DNA Res. 2007;14:169-181.

11. Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA. 2012;307:1959-1969.

12. Sharma V, Garg S, Aggarwal S. Probiotics and liver disease. J Appl Microbiol. 2013;24:147-163.

13. He T, Priebe MG, Zhong Y, et al. Effects of yogurt and bifidobacteria supplementation on the colonic microbiota in lactose-intolerant subjects. J Appl Microbiol. 2007;104:595-604.

14. Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. Gastroenterology. 2000;119:305-309.

15. Kajander K, Mylllyluoma E, Rajilič-Stojanović M, et al. Clinical trial: multispecies probiotic supplementation alleviates the symptoms of irritable bowel syndrome and stabilizes intestinal microbiota. Aliment Pharmacol Ther. 2008;27:48-57.

16. Ritchie ML, Romanuk TN. A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS One. 2012;7:e34938.

17. Gibson RJ, Keefe DM, Lalla RV, et al; Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of agents for the management of gastrointestinal mucositis in cancer patients. Support Care Cancer. 2013;21:313-326.

18. Urbanček H, Kazar T, Mezes I, Neumann K. Results of a double-blind, randomized study to evaluate the efficacy and safety of Antiophilus in patients with radiation-induced diarrhoea. Eur J Gastroenterol Hepatol. 2001;13:391-396.

19. Delia P, Sansotta G, Donato V, et al. Use of probiotics for prevention of radiation-induced diarrhea. World J Gastroenterol. 2007;13:912-915.

20. Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev. 2010;(11):CD003048.

21. Barton LL, Rider ED, Coen RW. Bacteremic infection with Pediococcus: vancomycin resistant opportunistic. Pediatrics. 2001;107:775-776.

22. De Groote MA, Frank DN, Dowell E, Glode MP, Pace NR. Lactobacillus rhamnosus GG bacteremia associated with probiotic use in a child with short gut syndrome. Pediatr Infect Dis J. 2005;24:278-280.

23. Ledoux D, Labombardi VJ, Karter D. Lactobacillus acidophilus bacteremia after use of a probiotic in a patient with AIDS and Hodgkin’s disease. Int J STD AIDS. 2006;17:280-282.

24. Richard V, Van der Auwera P, Snoeck R, Daneau D, Meunier F. Nosocomial bacteremia caused by Bacillus species. Eur J Clin Microbiol Infect Dis. 1988;7:783-785.

25. Tommasi C, Equitani F, Masala M, et al. Diagnostic difficulties of Lactobacillus casei bacteremia in immunocompetent patients: a case report. J Med Case Rep. 2008;2:315.

26. Vahabnezhad E, Mochon AB, Wozniak LJ, Ziring DA. Lactobacillus bacteremia associated with probiotic use in a pediatric patient with ulcerative colitis. J Clin Gastroenterol. 2013;47:437-439.

27. Burkhartt O, Köhlnhein T, Pletz M, Welte T. Saccharomyces boulardii induced sepsis: successful therapy with voriconazole after treatment failure with fluconazole. Scand J Infect Dis. 2005;37:69-72.

28. Kunz AN, Noel JM, Fairchok MP. Two cases of Lactobacillus bacteremia during probiotic treatment of short gut syndrome. J Pediatr Gastroenterol Nutr. 2004;38:457-458.

29. Land MH, Rouster-Stevens K, Woods CR, Cannon ML, Cnota J, Shetty AK. Lactobacillus sepsis associated with probiotic therapy. Pediatr. 2005;115:178-181.

30. Lestin F, Pertschy A, Rimék D. Fungemia after oral treatment with Saccharomyces boulardii in a patient with multiple comorbidities. Dtsch Med Wochenshr. 2003;128:2531-2533.

31. Oggioni MR, Pozzi G, Valensin PE, Galiens P, Bigazzi C. Recurrent septicemia in an immunocompromised patient due to probiotic strains of Bacillus subtilis. J Clin Microbiol. 1998;36:325-326.

32. Ohishi A, Takahashi S, Ito Y, et al. Bifidobacterium septicemia associated with postoperative probiotic therapy in a neonate with omphalocele. J Pediatr. 2010;156:679-681.

33. Zein EF, Karaa S, Chemaly A, Saidi I, Daou-Chahine W, Rohban R. Lactobacillus rhamnosus septicemia in a diabetic patient with omphalocele. J Clin Diagn Res. 2013;7:338-339.

34. Zeki EF, Chena S, Saval H, Saacid I, Daou-Chahine W. Lactobacillus rhamnosus septicemia in a diabetic patient with omphalocele. J Clin Diagn Res. 2013;7:338-339.

35. Muñoz P, Bouza E, Cuenca-Estrella M, et al. Saccharomyces cerevisiae fungemia: an emerging infectious disease. Clin Infect Dis. 2005;40:1625-1634.

36. Velicer CM, Ulrich CM. Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review. J Clin Oncol. 2008;26:665-673.

37. Vickers KA, Jolly KB, Greenfield SM. Herbal medicine: women's views, knowledge and interactions with doctors: a qualitative study. BMC Complement Altern Med. 2006;6:40.
genetic predisposition to mammary cancer in mice. *Int J Cancer*. 2014;135:529-540.

38. Aragón F, Carino S, Perdigón G, de Moreno de LeBlanc A. The administration of milk fermented by the probiotic *Lactobacillus casei* CRL 431 exerts an immunomodulatory effect against a breast tumour in a mouse model. *Immunobiology*. 2014;219:457-464.

39. Mohania D, Kansal VK, Kruzliak P, Kumari A. Probiotic dahi containing *Lactobacillus acidophilus* and *Bifidobacterium bifidum* modulates the formation of aberrant crypt foci, mucin-depleted foci, and cell proliferation on 1,2-dimethylhydrazine-induced colorectal carcinogenesis in Wistar rats. *Rejuvenation Res*. 2014;17:325-333.

40. Cesaro S, Chinello P, Rossi L, Zanesco L. *Saccharomyces cerevisiae* fungemia in a neutropenic patient treated with *Saccharomyces boulardii*. *Support Care Cancer*. 2000;8:504-505.

41. Fruchart C, Salah A, Gray C, et al. Lactobacillus species as emerging pathogens in neutropenic patients. *Eur J Clin Microbiol Infect Dis*. 1997;16:681-684.

42. Mego M, Ebringer L, Drgona L, et al. Prevention of febrile neutropenia in cancer patients by probiotic strain *Enterococcus faecium* M-74: pilot study phase I. *Neoplasma*. 2005;52:159-164.

43. Schultz M, Baranchi A, Thurston L, et al. Consumer demographics and expectations of probiotic therapy in New Zealand: results of a large telephone survey. *NZ Med J*. 2011;124:36-43.

44. Mego M, Koncekova R, Mikuskova E, et al. Prevention of febrile neutropenia in cancer patients by probiotic strain *Enterococcus faecium* M-74: phase II study. *Support Care Cancer*. 2006;14:285-290.

45. Fuccio L, Guido A, Eusebi LH, et al. Effects of probiotics for the prevention and treatment of radiation-induced diarrhea. *J Clin Gastroenterol*. 2009;43:506-513.

46. Mego M, Chovanec J, Vochyanova-Andrezalova I, et al. Prevention of irinotecan induced diarrhea by probiotics: a randomized double blind, placebo controlled pilot study. *Complement Ther Med*. 2015;23:356-362.

47. Cassileth BR, Heitzer M, Wesa K. The public health impact of herbs and nutritional supplements. *Pharm Biol*. 2009;47:761-767.