Introducing Our New Open Access Format

Marianne Trevorrow,[1] MA, ND

On June 1, we changed the *CAND Journal*'s publishing model from subscription-based to open access, removing all barriers to open science on our digital platform.

What this means for readers is that all articles published in this edition and from now on are freely available immediately under a Creative Commons Attribution-NonCommercial 4.0 license (CC BY-NC 4.0). This allows readers to download, share, and adapt our content for non-commercial purposes, provided proper credit is given.[1]

In order to prevent financial obstacles to publishing naturopathic research, we also won't be adding publication or "processing" fees, which many journals charge authors to keep their articles outside of paywalls. This means that once their work is published in the *CAND Journal*, authors are free to distribute, reproduce, or archive their work (as long as they cite us as the original publisher), contributing to increased knowledge and a greater impact of naturopathic literature globally.

At the *CAND Journal*, this is our contribution to the Canadian Association of Naturopathic Doctors' (CAND's) 2025–2028 Strategic Plan, which emphasizes collaboration with the larger healthcare community and the understanding that we are part of a science-based profession that promotes the use of research and evidence in our clinical practices, while holding space for traditional medicines and wisdom. They have provided us with the additional support to make this project happen and are continuing to underwrite this publication as they have been since our inception.

This transition also marks the end of a multi-month process of reviewing and updating our guidelines to accommodate the increasing number of research articles we receive, as well as formulating new standards for the use of artificial intelligence (AI) in the process of creating and documenting research. At this point in our evolution, it made sense to share the knowledge available to our members with the wider public and to contribute to the broader conversation(s) on improving access to primary health care in Canada in the 21st century.

Ellen Conte, ND, a Research Associate at the Canadian College of Naturopathic Medicine and the Patterson Institute for Integrative Oncology Research, member of the *CAND Journal* Editorial Board, and frequent contributor to this journal, is our guest editor for this special edition. She will introduce our content for the edition, which is entirely focused on research in naturopathic cancer care. She also played an important behind-the-scenes role in soliciting content when we began planning this second special edition last summer.

As always, we welcome feedback about our recent changes and ask our colleagues to consider helping us grow by contributing to the *CAND Journal* in the future.

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I have read and understood the *CAND Journal*'s policy on conflicts of interest and declare that I have none.

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The Value of Naturopathic Medicine in Cancer Care

Ellen Conte, ND

An estimated 45% of Canadians will be diagnosed with cancer in their lifetime.[1] This striking statistic highlights the need for all healthcare providers, including naturopathic doctors (NDs), to prioritize and maintain a working knowledge in cancer prevention and supportive care. This special issue of the *CAND Journal* features research in naturopathic cancer care, which holds relevance for the greater naturopathic and traditional, complementary, and integrative medicine (TCIM) communities.

While the mainstay of cancer treatment is conventional medical care, NDs and other TCIM practitioners can play an important role in cancer prevention, supportive treatment, and survivorship care. An estimated 33% to 35% of cancers diagnosed in Canada could be prevented through modifiable risk factors, including tobacco smoking, physical inactivity, excess body weight, low fruit and vegetable intake, and alcohol intake.[2] The number of cancers caused by such risk factors and others is expected to rise over the coming decades.[2] Given the strong focus naturopathic medicine places on prevention[3] and lifestyle practices,[4] NDs are well suited to help curb the rising rates of cancer.

Among people with cancer, rates of utilization of TCIM are high,[5] with patients seeking care for various reasons including improving cancer outcomes, treating symptoms, addressing holistic needs, improving general health, and empowering themselves.[5] Evidence supporting the use of TCIM strategies during cancer treatment is growing,[6] which has resulted in the emergence of clinical practice guidelines,[7-10] the Oncology Association of Naturopathic Physicians Principles of Care guideline,[11] and a formal definition of integrative oncology.[12] Naturopathic doctors, particularly those with additional training in cancer care, are well equipped to safely and effectively integrate complementary strategies alongside conventional cancer treatment.

Finally, although cancer remains the leading cause of death in Canada, mortality rates are declining, resulting in a greater number of cancer survivors.[13] Current estimates indicate about 1.5 million Canadians are cancer survivors who will live for 25 or more years beyond their diagnosis.[13] It is recognized that the growing number of cancer survivors necessitates increased support for the long-term health and quality of life for these individuals. Post-treatment, people may experience lingering side effects, late effects of treatment (e.g., osteoporosis, infertility), mental and emotional challenges, and concerns about cancer recurrence. Naturopathic medicine, with its focus on whole person–centred care and lifestyle practices,[4,11] can play a valuable role in the complex field of survivorship navigation and care. While it is understandable, and perhaps advisable, that NDs who focus on general care or other focused areas may choose not to provide care for people with active cancer, most NDs can provide support for cancer prevention and survivorship.

This special issue on cancer care features three submissions. Two papers, published by Standish et al. and Seely et al., report results from the large observational study called the Canadian US Integrative Oncology Study (CUSIOS). This study is a collaboration between the Canadian College of Naturopathic Medicine and Bastyr University. For transparency, I am a coauthor on these papers. The first paper describes survival of patients with advanced breast, colorectal, ovarian, and pancreatic cancer who sought care from a naturopathic doctor at a participating clinic. Survival was compared with that of matched patients from the United States' Surveillance, Epidemiology, and End Results Program. The discussion of the methods and interpretation are valuable reads to understand the intricacies, challenges, and opportunities with this type of research. The second paper describes the treatment provided by NDs to enrolled participants and provides the most comprehensive description of naturopathic cancer care to date, highlighting the breadth of treatments NDs utilize when caring for those with cancer.

Sandri and Landers wrote a narrative review of naturopathic care for those with prostate cancer under active surveillance, using data from clinical and observational studies. This review offers actionable and evidence-informed strategies which can support people during a time when active medical management is not indicated.

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Given the high prevalence of cancer and survivorship, the unique and holistic needs of those impacted, and the growing body of evidence supporting the use of integrative therapies, this issue will hopefully be of relevance to the naturopathic community.

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Naturopathic Oncology for Advanced Cancers: Survival Outcomes from the Canadian/US Integrative Oncology Study

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ABSTRACT

Background: Several traditional, complementary, and integrative therapies have been studied for their effect on cancer outcomes; however, few studies have evaluated naturopathic oncology in a real-world setting. We conducted an observational cohort study to evaluate whether consulting with a naturopathic doctor (ND) improves survival in people with advanced cancers.

Methods: Participants with metastatic breast, metastatic colorectal, advanced ovarian, or advanced pancreatic cancer were recruited from 12 North American naturopathic clinics. The primary outcome was 5-year overall survival compared with a matched cohort from the Surveillance Epidemiology and End Results (SEER) registry. We additionally evaluated survival based on the number of ND visits and intravenous vitamin C (IVC), intravenous mistletoe, and hyperthermia treatments.

Results: 400 participants were enrolled: 165 had breast cancer, 116 had colorectal cancer, 72 had ovarian cancer, and 47 had pancreatic cancer. A bootstrapped analysis showed no significant differences in 5-year survival compared with SEER (breast: median hazard ratio [HR] 1.10, 95% confidence interval [CI] 0.80–1.54; colorectal: median HR 0.95, 95% CI 0.68–1.31; ovarian: median HR 1.08, 95% CI 0.64–1.86; pancreatic: median HR 0.76, 95% CI 0.51–1.13). Higher survival odds were seen with increasing IVC treatments in breast cancer, and with increasing ND visits in all cancer types except ovarian.

Conclusion: No survival benefits were seen in patients with advanced cancers who saw an ND compared with registry data. After controlling for survivorship bias, in general, the number of ND visits positively correlated with improved survival; however, the number of select naturopathic treatments did not. Findings should be interpreted with caution given study limitations.

Key Words Naturopathic medicine, integrative medicine, integrative oncology, naturopathic care, cancer survival, naturopathic doctor, naturopathic physician

INTRODUCTION

Despite advances in cancer screening and treatment, mortality remains high. In 2022, nearly 10 million people worldwide died from cancer.[1] In Canada and the United States, cancer is the first and second leading cause of death, respectively.[2,3] Innovative approaches are needed to improve survival rates.

Traditional, complementary, and integrative medicine (TCIM) is commonly used by people with cancer, with rates of use ranging from 40 to 80%.[4-6] In North America, naturopathic medicine is a system of care provided by naturopathic doctors (NDs) that is recognized as part of the TCIM umbrella and includes the use of nutritional advice, dietary supplements, botanical medicine, nutrient and phytopharmaceutical injection therapy, acupuncture, counselling and emotional support, and lifestyle modifications.[7] Naturopathic medicine is one of the most commonly practiced systems of TCIM in the Western world,[8] with approximately 8,000 licensed NDs in North America.[9] Studies suggest naturopathic medicine use is higher among those with cancer than the general population.[8]

Existing research on naturopathic medicine in cancer has typically focused on specific therapies, and outcomes related to quality of life (QOL) and symptom burden over survival.[10] Some interventions have demonstrated improvements in survival for patients with cancer, including *Trametes versicolor* (turkey tail mushroom),[11] *Viscum album* (mistletoe extract),[12] exercise,[13] and the Mediterranean Diet.[14,15] Although evidence is increasing, most studies have focused

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on single agents in isolation, which does not accurately reflect naturopathic medicine's holistic and multimodal real-world application in cancer care. Few studies have evaluated survival outcomes for patients with advanced cancer receiving naturopathic care in a pragmatic setting. Evidence supporting benefits is currently limited,[16,17] highlighting the need for additional research.

The Canadian/US Integrative Oncology Study (CUSIOS) is an observational cohort study with the overarching goal of studying naturopathic oncology in a real-world setting. The primary objective was to measure survival in patients with late-stage breast, colorectal, ovarian, or pancreatic cancer who consulted with an ND. Five-year overall survival was compared with matched comparators from the Surveillance Epidemiology and End Results (SEER) database. Secondary objectives included describing the scope of treatments recommended to patients by NDs, comparing survival amongst enrolled participants based on the number of ND visits and the frequency of use of verifiably received naturopathic treatments, collecting health-related QOL data, estimating costs of naturopathic cancer care, and gathering information on participants' qualitative experience of care. Data on the scope of ND recommendations, QOL, cost, and qualitative experiences are not discussed here and will be reported in separate publications.

In this paper, we compare 5-year survival outcomes of patients with advanced cancers who received naturopathic care with SEER as an external comparator. We also compare survival internally among enrolled participants based on the number of ND visits and naturopathic treatments received. We hypothesized that overall survival for participants enrolled in this study would be superior to what is reported by SEER.

METHODS

This paper was written alongside our reports on cost, QOL, qualitative experiences, and the type and frequency of ND recommendations to study participants.[18] Many of the study methods were developed independently of the study outcomes; thus, there will be significant overlap.

Study Design

This was an observational study of patients with advanced breast, colorectal, ovarian, or pancreatic cancer who consulted an ND in North America. Recruitment and follow-up were primarily prospective; however, there were no restrictions based on date of diagnosis or enrollment date relative to the participant's first visit with their ND. Thus, participants had varying levels of retrospective data collection. Clinics were requested to approach all eligible patients; however, we did not have a method to verify consecutive recruitment.

Setting

The study was conducted at 12 outpatient naturopathic clinics located in Canada (n = 5) and the United States (US) (n = 7). The primary coordinating centres were the Bastyr Center for Natural Health in Seattle, Washington, and The Centre for Health Innovation in Ottawa, Ontario. Additional sites were: Integrated Health Clinic Cancer Care Centre, Fort Langley, British Columbia; Marsden Centre for Excellence in Integrative Medicine, Vaughan, Ontario; Health Source Integrative Medical Centre, Kitchener, Ontario; Vital Victoria Naturopathic Clinic, Victoria, British Columbia; Naturopathic Specialists LLC, Scottsdale, Arizona; Salish Care Center, Fife, Washington; Hawaii Integrative Oncology, Kailua-Kona, Hawaii; Tree of Health Integrative Medicine, Woodinville, Washington; Seattle Integrative Cancer Center, Seattle, Washington; Advanced Integrative Medical Science Institute, Seattle, Washington. Clinics were selected for their focus in cancer care and NDs with a depth of experience in the field. A total of 29 NDs provided care to at least one study participant. All NDs had experience in a cancer care setting, and 15 were Fellows of the American Board of Naturopathic Oncology.

Participants

Eligible participants were adults 18 years of age or older who presented for care to a participating clinic with a confirmed diagnosis of one of the following:

- Metastatic breast cancer (*de novo* stage IV or recurrent)
- Metastatic colorectal cancer (*de novo* stage IV or recurrent)
- Advanced ovarian cancer (stage III or IV, *de novo* or recurrent)
- Advanced pancreatic cancer (stage III or IV, *de novo* or recurrent)

Stages were determined per the American Joint Committee on Cancer's staging guidelines (version 7). Participants additionally had to be a citizen or permanent resident of the country in which they were receiving treatment. All participants signed an informed consent form prior to participating. Recruitment began in June 2015 and concluded in March 2020. Participants were followed for at least 2 years and up to 3 years. Variable follow-up time occurred due to funding restraints, which arose due to a longer than anticipated recruitment period. All participants were offered a $200 stipend upon enrolment to be used towards any practitioner consultation at the participant's naturopathic clinic.

Naturopathic Care

Participants received treatment from their ND independent of this research study. All recommendations made by NDs to patients on this study were collected and are reported in a separate manuscript.[18] In brief, recommendations spanned various modalities of treatment within the ND scope of practice, including natural health products, nutrition advice, intravenous (IV) and injectable therapies, physical medicine and body-based therapies, prescription and over-the-counter medications, mental health, Traditional Chinese Medicine, and hyperthermia.

Regulatory Adherence

Ethics approval was obtained from the Research Ethics Board of the Canadian College of Naturopathic Medicine and the Institutional

Review Board at the Office of Research Integrity at Bastyr University prior to study initiation. The study was registered with clinicaltrials.gov, NCT02494037.

Outcomes

The primary study outcome was 5-year overall survival compared with a matched cohort from the SEER database. As a secondary outcome, we compared survival rates among study participants based on the number of ND visits and the frequency of use of verifiably received naturopathic treatments, including intravenous vitamin C (IVC), IV mistletoe, and hyperthermia.

Data Sources

Cancer treatments and clinical data were collected from naturopathic clinic records and conventional medical records. Naturopathic clinic records were reviewed from the first visit until the study end date, and conventional records were reviewed from diagnosis until the study end date. Date of death was collected from medical chart review and obituary searches. For US participants, the National Death Index was also queried. Last known survival date was collected from medical records if survival status was unknown. SEER data were obtained from SEER*Stat 8.4 and included patients diagnosed from 2010 to 2019.

Sample Size

The total expected study sample size was 400 patients, of which it was estimated 150 would have breast cancer, 150 would have colorectal cancer, 50 would have ovarian cancer, and 50 would have pancreatic cancer. The sample size was determined based on pragmatic considerations related to the number of estimated eligible patients the sites would see, the expected rate of enrollment, study duration, and available funding.

Quantitative Variables

Survival time for our population was defined as the date of stage III or IV diagnosis until study completion. Participants who were diagnosed at stage III but progressed to stage IV prior to enrolment were classified as stage IV; participants who were diagnosed at stage III but progressed to stage IV after enrolment were classified as stage III. Study completion was defined as occurring 3 years after a participant's first visit to a study clinic, death, end of study, or date of last known survival. Participants were only included in the primary survival analysis if their date of diagnosis occurred in 2010 or later, as SEER does not report some key variables prior to 2010. In cases where the date of diagnosis was not fully known (i.e., only month or year), the dates were adjusted using the "Date of Diagnosis" algorithm described in the SEER Program Coding and Staging Manual 2023.[19] Although 5-year overall survival was the primary outcome, some patients had survival times longer than 5 years depending on the lag time between date of diagnosis and the first visit with their ND. For these participants, survival time was truncated at 5 years.

Naturopathic treatments were abstracted from naturopathic clinic records and separated into distinct categories using the Research Electronic Data Capture (REDCap) platform. Entries were verified by a second team member. Variables for the internal survival comparison included the number of visits with an ND, and the number of IVC, IV mistletoe, and hyperthermia treatments. These treatments were chosen because they were more invasive and costly relative to other naturopathic oncology treatments, they had a high frequency of use in our population, and we were able to assess compliance given they were administered in-clinic. Data were only included if we could verifiably determine that participants received treatments at one of the study clinics (i.e., data on treatments received at other clinics or centres were not collected).

Statistical Methods

To analyze 5-year survival, we compared study participants with matched comparators from the SEER registry using sex, age, year of diagnosis, histology, hormone receptor status (breast cancer only), and cancer stage as matching variables. Each cancer type was analyzed separately. Participants were matched on all applicable variables and, additionally, were only matched if their lag time between date of diagnosis and date of study enrolment was less than a SEER patient's survival time. Survival was analyzed using a bootstrap method. One randomly selected matched SEER patient was included for each study participant to create a cohort of equal size. A hazard ratio (HR), confidence interval (CI), and P value were generated using the Cox proportional hazards model. This analysis was run 10,000 times, each time randomly selecting one matched SEER patient for each study participant. The median HR and CI for all 10,000 outputs were used to determine statistical significance. We additionally conducted post-hoc sub-group analyses for each cancer type. In the first, we only included study participants whose lag time was less than or equal to the median lag time of participants with that cancer type (i.e., short lag time). In the second, we only included study participants who were diagnosed with *de novo* stage III or IV disease. Ovarian cancer was omitted from this analysis given more than 90% of participants were diagnosed *de novo*. In the third, we only included study participants who had a short lag time and were diagnosed *de novo*. Median lag times for each cancer type were as follows:

- Breast: 6 months
- Colorectal: 6 months
- Ovarian: 8 months
- Pancreatic: 2 months

Bootstrapped analyses are meant to generate a distribution of statistics to estimate confidence intervals. Calculating a single P value is therefore not necessary and provides less information than the confidence intervals. Results were considered significant if the confidence interval did not cross 1.00. Hazard ratios < 1.00 indicate a beneficial effect for study participants.

Independently of the bootstrapped analyses, Kaplan-Meier curves were created to visually represent the data for each cancer type. Each curve contained three cohorts: (1) all SEER patients with the appropriate cancer type (SEER), (2) a small group of matched SEER patients (SEER(M)), and (3) study participants

(CUSIOS). The matched SEER group curves were created by randomly selecting several matched patients per study participant, with the number selected equalling the lowest number of matches of all the study participants in the given group (e.g., if the lowest number of matches was 4, then 4 SEER patients were included for each study participant). As the Kaplan-Meier curves were created as a visual representation of the data, no statistical analyses were applied. The complete bootstrapped analysis provides the best estimate for the confidence intervals.

Survival based on the type and frequency of naturopathic treatments received was conducted using a time varying covariate analysis and the log rank test. Univariable and multivariable models were constructed using the number of IVC, IV mistletoe, and hyperthermia treatments, number of ND visits, sex, age, histology, cancer stage, and hormone receptor status (breast cancer only) as covariates. Exact dates were used for ND visits, and time points of 3, 6, 9, 12, 18, 24, 30, and 36 months used for IVC, IV mistletoe, and hyperthermia treatments. Locoregional hyperthermia and whole-body hyperthermia were combined to increase power for this analysis. Results are presented showing the effect of the median number of treatments received.

Finally, some variables were analyzed using frequency distributions and descriptive statistics. Standard deviation was used as a method of dispersion for mean values. Inter-quartile range (IQR) or range was used as a method of dispersion for median values.

Data Availability Statement

Datasets used in this study are available by request only. Please contact Dugald Seely, dseely@thechi.ca, if you would like to request access to any datasets.

RESULTS

Participant Characteristics

In total, 400 patients were enrolled. Figure 1 shows participant flow throughout the study and Table 1 summarizes baseline clinical status and demographic characteristics for all cancer types.

Breast Cancer

One hundred sixty-five participants had breast cancer. Eleven were found to be ineligible after enrolment and were not included in any analyses. The median time from participants' diagnosis to

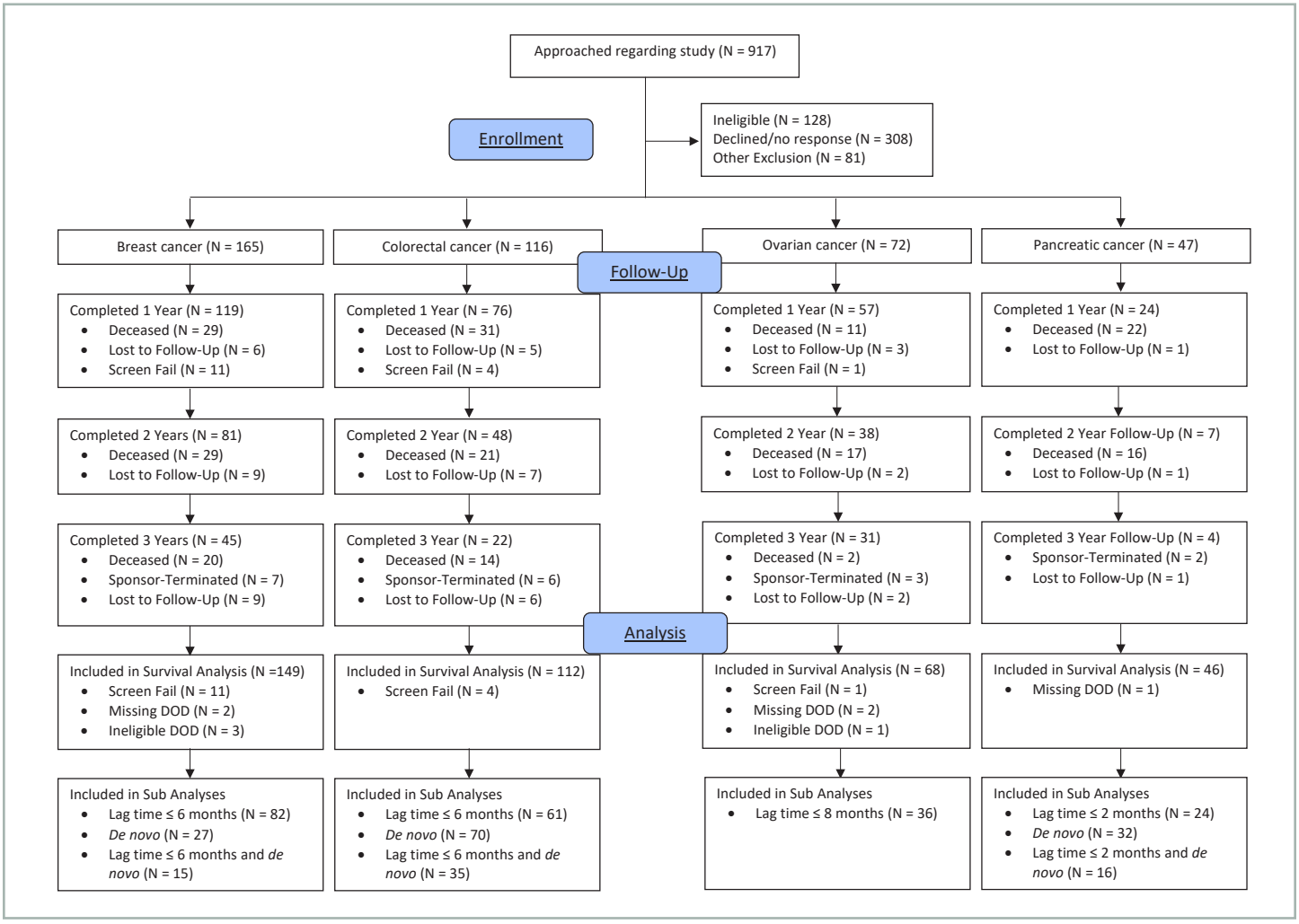

FIGURE 1 Participant Flow Diagram. Patients were only recorded as approached if an investigator believed they were eligible for the study and if the patient was interested in participating. Screen fail: patient was enrolled in the study but was later found to be ineligible; DOD: date of death.

their first ND visit was 5 months (IQR 2–14). Median time from the first ND visit to enrolment was 1 month (IQR 0–3). Mean age at diagnosis was 53.4 ± 12.0 years. 74% of participants had a ductal carcinoma; 16% had a lobular carcinoma. 83% were estrogen or progesterone receptor positive, and 11% were human epidermal growth factor receptor positive.

Colorectal Cancer

One hundred sixteen participants had colorectal cancer. Four were found to be ineligible after enrolment and were not included in any analyses. The median time from participants' diagnosis to their first ND visit was 5 months (IQR 2–19). Median time from the first ND visit to enrolment was 1 month (IQR 0–3). Mean age at diagnosis was 55.8 ± 11.9 years. All participants had adenocarcinoma histology.

Ovarian Cancer

Seventy-two participants had ovarian cancer. One participant was found to be ineligible after enrolment and was not included in any analyses. The median time from participants' diagnosis to their first ND visit was 7 months (IQR 2–26). Median time from the first ND visit to enrolment was 1 month (IQR 0–3). Mean age at diagnosis was 58.6 ± 10.6 years. 83% of participants had a serous carcinoma; 17% were classified as "other" histology. At the time of enrolment, 36 participants (51%) had stage III disease and 35 (49%) had stage IV. All participants with stage III disease were diagnosed *de novo*. Of those with stage IV disease, 26 (74%) were diagnosed *de novo*.

Pancreatic Cancer

Forty-seven participants had pancreatic cancer. The median time from participant diagnosis to their first ND visit was 1 month (IQR 1–7). Median time from the first ND visit to enrolment was 1 month (IQR 0–2). Mean age at diagnosis was 62.0 ± 11.6 years. 91% of participants had adenocarcinoma histology; 9% were classified as "other." At the time of enrolment, 14 participants (30%) had stage III disease and 33 (70%) had stage IV. Of those with stage III disease, 13 (93%) were diagnosed *de novo*. Of those with stage IV disease, 19 (58%) were diagnosed *de novo*.

TABLE 1 Clinical Status and Demographics

Characteristic	Breast Cancer (*n* = 154)	Colorectal Cancer (*n* = 112)	Ovarian Cancer (*n* = 71)	Pancreatic Cancer (*n* = 47)
Sex				
Male	0	45%	0	49%
Female	100%	55%	100%	51%
Cancer stage				
Stage III	N/A	N/A	51%	30%
Stage IV	100%	100%	49%	70%
ECOG				
0, 1, 2	91%	100%	100%	100%
3, 4	9%	0	0	0
Sites of Metastasis[1,2]				
Bone	69%	7%	12%	3%
Lymph Nodes	37%	31%	32%	26%
Liver	36%	68%	29%	77%
Lung	29%	43%	24%	29%
Brain	9%	0	3%	3%
Number of Sites of Metastases[2]				
1 site	33%	35%	41%	47%
2 sites	27%	27%	29%	34%
3 sites	16%	21%	15%	13%
4+ sites	24%	17%	15%	6%
Hormone Receptor Status				
Luminal A (ER+ or PR+, HER2-)	78%	N/A	N/A	N/A
Luminal B (ER+ or PR+, HER2+)	5%	N/A	N/A	N/A
Triple Negative (ER-, PR-, HER2-)	11%	N/A	N/A	N/A
HER2 enriched (ER-, PR-, HER2+)	6%	N/A	N/A	N/A

[1] Not all sites of metastasis shown; multiple selections permitted; [2] Only includes participants diagnosed with stage IV disease.
ECOG=Eastern Cooperative Oncology Group score; ER=estrogen receptor; HER=human epidermal growth factor receptor; PR=progesterone receptor.

External Survival Comparison – SEER

Breast Cancer

Of the 165 participants with breast cancer, 149 were included in the primary survival analysis (see Figure 1 for exclusions). From SEER, there were 35,551 patients with stage IV breast cancer diagnosed in 2010 or later, 14,049 (40%) of whom matched with at least one study participant. Figure 2 shows survival results for SEER data compared with all 149 study participants. Survival favoured the SEER group but was not statistically significant (median HR 1.10, 95% CI 0.80–1.54). 894 patients were used to generate the matched SEER curve (least number of matches = 6).

In the subset of study participants who had a lag time between diagnosis and enrolment of 6 months or less (n = 82), survival favoured study participants but was not statistically significant (median HR 0.82, 95% CI 0.52–1.31). In the subset of study participants who were diagnosed with *de novo* stage IV disease (n = 27), survival favoured study participants but was not statistically significant (median HR 0.81, 95% CI 0.35–1.91). In the subset of study participants who were diagnosed with *de novo* stage IV disease and had a lag time between diagnosis and enrolment of 6 months or less (n = 15), survival favoured study participants but was not statistically significant (median HR 0.69, 95% CI 0.20–2.47). Kaplan Meier curves for each sub-analysis can be found in Appendix A, Figures A1–A3.

Colorectal Cancer

Of the 116 participants with colorectal cancer, 112 were included in the primary survival analysis (see Figure 1 for exclusions). From SEER, there were 71,735 patients with stage IV colon or rectal cancer diagnosed in 2010 or later, 22,156 (31%) of whom matched with at least one study participant. Figure 3 shows survival results for SEER data compared with all 112 participants. Survival did not favour either group (median HR 0.95, 95% CI 0.68–1.31). 2,688 patients were used to generate the matched SEER curve (least number of matches = 24).

In the subset of study participants whose lag time between diagnosis and enrolment was 6 months or less (n = 61), survival favoured study participants but was not statistically significant (median HR 0.64, 95% CI 0.40–1.04). In the subset of study participants who were diagnosed with *de novo* stage IV disease (n = 70), survival did not favour any group (median HR 0.99, 95% CI 0.66–1.49). In the subset of study participants who were diagnosed with *de novo* stage IV disease and had a lag time between diagnosis and enrolment of 6 months or less (n = 35), survival favoured study participants but was not statistically significant (median HR 0.63, 95% CI 0.32–1.21). Kaplan Meier curves for each sub-analysis can be found in Appendix A, Figures A4–A6.

Ovarian Cancer

Of the 72 participants with ovarian cancer, 68 were included in the primary survival analysis (see Figure 1 for exclusions). From SEER, there were 32,487 patients with stage III or IV ovarian cancer diagnosed from 2010 to 2019 or later, 7,101 (22%) of whom matched with at least one study participant. The bootstrapped survival analysis showed no significant differences between study participants and SEER (median HR 1.08, 95% CI 0.64–1.86). Figure 4 shows a Kaplan Meier curve for all study participants. 340 patients were used to generate the matched SEER curve (least number of matches = 5).

In the subset of study participants who had a lag time between diagnosis and enrolment of 8 months or less (n = 36), the bootstrapped survival analysis showed no significant differences between study participants and SEER (median HR 0.98, 95% CI 0.47–2.11). Appendix A, Figure A7 shows the Kaplan Meier curve for this subset.

As per the study methods, ovarian cancer was omitted from any analyses involving *de novo* disease, given more than 90% of participants were diagnosed *de novo*.

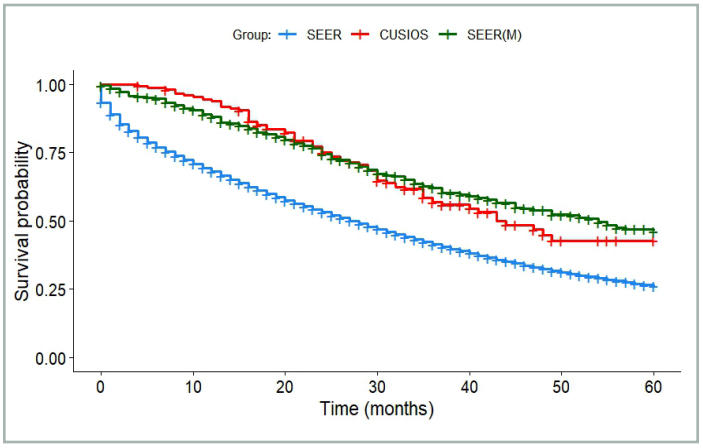

FIGURE 2 Breast Cancer Survival. SEER: All patients from SEER with stage IV breast cancer (N = 35,551). SEER(M): Patients from SEER who matched with at least one study participant (N = 894). CUSIOS: Study population (N = 149). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results (registry data); CUSIOS: Canadian/US Integrative Oncology Study (study population).

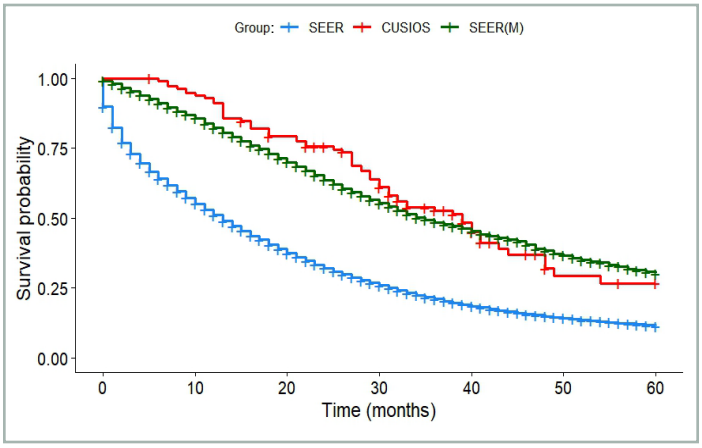

FIGURE 3 Colorectal Cancer Survival. SEER: All patients from SEER with stage IV colorectal cancer (N = 71,735). SEER(M): Patients from SEER who matched with at least one study participant (N = 2,688). CUSIOS: Study population (N = 112). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results (registry data); CUSIOS: Canadian/US Integrative Oncology Study (study population).

Pancreatic Cancer

Of the 47 participants with pancreatic cancer, 46 were included in the primary survival analysis (see Figure 1 for exclusions). From SEER, there were 65,851 patients with stage III or IV pancreatic cancer diagnosed in 2010 or later, 15,075 (23%) of whom matched with at least one study participant. Figure 5 shows survival results for SEER data compared with all 46 study participants. Survival favoured study participants but was not statistically significant (median HR 0.76, 95% CI 0.51–1.13). 552 patients were used to generate the matched SEER curve (least number of matches = 12).

In the subset of study participants who had a lag time between diagnosis and enrolment of 2 months or less (n = 24), survival favoured study participants but was not statistically significant (median HR 0.62, 95% CI 0.29–1.14). In the subset of study participants who were diagnosed with *de novo* disease (n = 32), survival favoured study participants but was not statistically significant (median HR 0.79, 95% CI 0.49–1.29). In the subset of study participants who were diagnosed with *de novo* disease and had a lag time between diagnosis and enrollment of 2 months or less (n = 16), survival favoured study participants but was not statistically significant (median HR 0.70, 95% CI 0.24–1.51). Kaplan Meier curves for each sub-analysis can be found in Appendix A, Figures A8–A10.

Internal Survival Comparison – Treatment-Based

Table 2 shows the results from the treatment-based survival comparisons. Statistically significant improved survival odds were seen in participants with breast cancer who received more IVC treatments (HR 0.80, 95% CI 0.67–0.96, p = 0.02 for 13 additional treatments). Statistically significant improved survival odds were also seen in participants with breast, colorectal, and pancreatic cancer who saw their ND more often (breast: HR 0.75, 95% CI 0.58–0.98, p = 0.04 for 5 additional visits, colorectal: HR 0.72, 95% CI 0.55–0.93, p = 0.02 for 4 additional visits; pancreatic: HR 0.53, 95% CI 0.34–0.84, p = 0.008 for 5 additional visits). All results remained significant in the multivariate models. Intravenous mistletoe and hyperthermia treatments did not confer higher survival odds with increasing treatment numbers in either the univariate or multivariate models for any cancer type. A significant survival disadvantage was seen in the multivariate model for participants with ovarian cancer who received more hyperthermia treatments (HR 1.70, 95% CI 1.01–2.84, p = 0.05 for 12 additional treatments); however, this was not seen in the univariate model. Multivariate results are not shown in Table 2. Results from the multivariate analysis and HRs for a single additional treatment are presented in Appendix B.

Conventional Cancer Treatments

Table 3 shows the frequency of conventional cancer treatments received by participants. Almost all participants (99%) received some form of treatment either before or after they were enrolled. Four participants (1 breast cancer, 3 pancreatic cancer) did not receive any conventional cancer treatments.

DISCUSSION

In this multicentre North American observational study, we compared 5-year overall survival in patients with advanced and/or metastatic breast, colorectal, ovarian, or pancreatic cancer who consulted with an ND with SEER data. No significant differences were seen, including in multiple sub-group analyses of study participants who were diagnosed with *de novo* disease and who saw an ND shortly after their diagnosis. To our knowledge, this is the second study comparing the survival of patients with breast cancer receiving care from an ND with US registry data, and the first in patients with colorectal, ovarian, and pancreatic cancer. Researchers previously conducted a similar study assessing recurrence of breast cancer after primary treatment for earlier-stage disease, which showed no benefit in disease-free survival for patients receiving naturopathic care.[20]

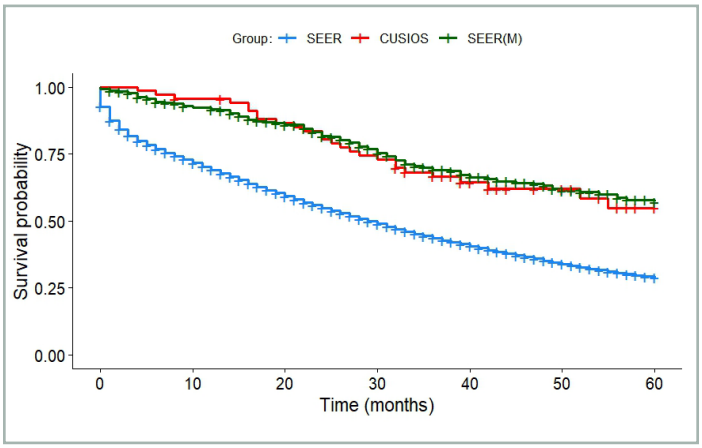

FIGURE 4 Ovarian Cancer Survival. SEER: All patients from SEER with stage III and IV ovarian cancer (N = 32,847). SEER(M): Patients from SEER who matched with at least one study participant (N = 340). CUSIOS: Study population (N = 68). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results (registry data); CUSIOS: Canadian/US Integrative Oncology Study (study population).

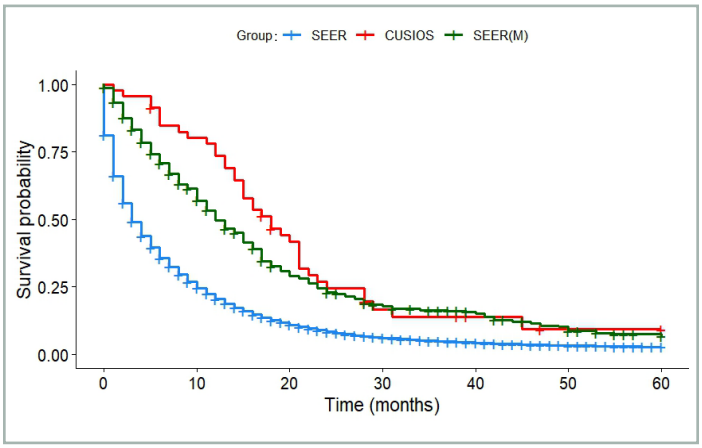

FIGURE 5 Pancreatic Cancer Survival. SEER: All patients from SEER with stage III or IV pancreatic cancer (N = 65,851). SEER(M): Patients from SEER who matched with at least one study participant (N = 552). CUSIOS: Study population (N = 46). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results

Although no results from the SEER comparison were statistically significant, there are a few findings which are notable. Firstly, survival favoured study participants with pancreatic cancer with consistent hazard reductions across the main analysis and all sub-analyses. This is hypothesis-generating for future research, particularly given the small sample size for this cohort of patients. Secondly, across all 4 cancer types, participants with shorter intervals between diagnosis and study enrolment demonstrated more favourable survival times compared with the overall cohort. Furthermore, this sub-analysis showed non-significant hazard reductions in participants with breast, pancreatic, and colorectal cancer. For ovarian cancer, it was equivocal. This suggests patients seeking naturopathic care long after they were diagnosed may be different from those who seek care more quickly. For example, they may have done so due to disease progression or increased symptom burden, which may not be the case for the SEER patients with whom they were matched. Additionally, patients receiving care late in their disease trajectory may have had less opportunity for naturopathic therapies to have a clinically meaningful effect. These confounders could bias outcomes in favour of SEER. Alternatively, patients who seek naturopathic care soon after they are diagnosed may be biased in favour of a greater preference for naturopathic care and a higher socioeconomic status, given that they are willing to pay privately to see an ND right away. This could bias outcomes in favour of study participants. It is also important to note that we do not have data on adherence to ND recommendations or other important confounders, such as smoking status and adherence to guideline-appropriate conventional care, which could heavily influence outcomes. Although the hazard reductions for those with shorter lag times are hypothesis-generating, we cannot make any definitive conclusions with the available data.

For some cancer types, survival trends differ for those with recurrent metastatic disease versus those diagnosed *de novo*. This is important as we included both groups of patients in our study, but SEER does not track progression. Thus, results will inherently be biased. For metastatic breast cancer, research has shown that patients with recurrent disease have worse survival outcomes than patients who are diagnosed *de novo*.[21] Given our population mostly had recurrent metastatic disease, this biases outcomes in favour of SEER. We saw more favourable outcomes in our *de novo* analysis for participants with breast cancer, which corroborates this bias. For patients with colorectal cancer, there are no reported differences between recurrent metastatic and *de novo* disease.[22] For patients with pancreatic cancer, research shows more favourable outcomes for those with recurrent metastatic disease,[23] which biases outcomes in favour of study participants. We did not see a difference between the main analysis and the *de novo* analysis for participants with pancreatic cancer, which suggests the bias may not have impacted this group.

We additionally compared survival among enrolled participants based on the number of naturopathic treatments received. Results indicated higher survival odds for participants receiving more ND visits if they had breast, colorectal, or pancreatic cancer. We also observed higher survival odds for participants receiving more IVC treatments if they had breast cancer. These results should be interpreted with caution, as the study was not specifically designed to

TABLE 2 Survival Based on Naturopathic Treatments

Treatment	Median Treatments	HR (95% CI)	P value	Participants	Received Treatment	Total Treatments
Breast Cancer						
IV vitamin C	13	0.80 (0.67–0.96)	0.02	134	67	2169
IV mistletoe	17.5	0.85 (0.61–1.20)	0.37	134	22	660
Hyperthermia	11.5	0.93 (0.68–1.28)	0.64	134	32	564
ND visits	5	0.75 (0.58–0.98)	0.04	150	150	996
Colorectal Cancer						
IV vitamin C	13	0.95 (0.79–1.14)	0.58	112	58	1189
IV mistletoe	12.5	0.92 (0.70–1.20)	0.53	112	28	538
Hyperthermia	15	0.94 (0.74–1.19)	0.60	112	35	795
ND visits	4	0.72 (0.55–0.93)	0.02	112	112	996
Ovarian Cancer						
IV vitamin C	17	0.97 (0.72–1.30)	0.81	68	31	831
IV mistletoe	11	0.85 (0.54–1.33)	0.49	68	15	315
Hyperthermia	12	1.30 (0.91–1.85)	0.14	68	15	257
ND visits	5	0.87 (0.61–1.26)	0.47	68	68	463
Pancreatic Cancer						
IV vitamin C	5	0.98 (0.90–1.08)	0.75	46	21	324
IV mistletoe	7.5	0.95 (0.71–1.27)	0.71	46	10	146
Hyperthermia	12.5	0.93 (0.71–1.22)	0.57	46	14	259
ND visits	5	0.53 (0.34–0.84)	0.008	46	46	250

Number of participants in each analysis varies due to missing data. CI=confidence interval; HR=hazard ratio; IV=intravenous; ND=naturopathic doctor.

TABLE 3 Conventional Cancer Treatments Received

Treatment	Breast Cancer (n = 154)	Colorectal Cancer (n = 112)	Ovarian Cancer (n = 71)	Pancreatic Cancer (n = 47)
Chemotherapy	81%	93%	99%	85%
Radiation therapy	77%	36%	18%	32%
Surgery	80%	72%	96%	34%
Hormone therapy	83%	0	8%	0
Monoclonal antibodies	51%	74%	38%	6%
Oral targeted therapy	54%	17%	30%	9%

evaluate these outcomes. Although we used a multivariate model to analyze the data, factors such as smoking status, socioeconomic status, and adherence to guideline-appropriate conventional care were once again not accounted for. The most noteworthy result is the positive correlation between number of ND visits and survival. A possible interpretation is that patients frequently seeing their ND may be more engaged in their treatment plan, and thus more likely to adhere to it. If this were true, it could suggest that those who more closely follow the recommendations of their NDs have improved survival outcomes compared with those who do not. While this is an interesting hypothesis, it relies on several assumptions and cannot be proven with the data available. Additionally, although the increase in survival with increasing IVC treatments in participants with breast cancer is encouraging, this effect was not seen in the other cancer types. There are currently no clinical trials evaluating IVC for survival outcomes in advanced breast cancer; however, there is supportive evidence for a survival advantage in metastatic pancreatic cancer[24] and RAS-mutated colorectal cancer,[25] which were not demonstrated herein. The number of hyperthermia treatments was negatively correlated with survival in the multivariate analysis of people with ovarian cancer; however, given these effects were not seen in the univariate model, it is likely not clinically significant. Finally, it is worth considering that people who choose to initiate IV therapy or hyperthermia may differ from those who do not. Those who choose these therapies may be doing so due to higher disease burden or progressive disease, which would negatively correlate with survival. Conversely, these individuals may have a higher socioeconomic status, which is often positively associated with survival. Because of this and the exploratory nature of the analysis, we cannot make any firm conclusions about the effect of naturopathic treatments on survival in our population.

Almost all participants received some form of conventional medical treatment either before or during the study. The frequency of use of these treatments in our population is comparable to, or higher than, population level data in the United States;[26-28] however, there is one notable exception. The rate of endocrine therapy usage in study participants with breast cancer is lower than what is typically seen in the United States (68% versus 84%, respectively).[27] These data are consistent with previous research that people with breast cancer receiving naturopathic care may be less likely to use endocrine therapy compared with those not receiving naturopathic care.[29] This may reflect different treatment preferences of patients who seek ND care. Given the importance of endocrine therapy in management of breast cancer, this may negatively impact survival outcomes.[30]

Justification for Analysis

The SEER registry was chosen as our comparator for survival and only included patients who matched with a study participant using the variables described above. This matching process provided over 14,000 patient comparators. Traditionally, our cohort would be directly compared with all matched patients in SEER; however, this introduces bias, given that SEER data are population-based and do not control for certain clinical characteristics known amongst our cohort. Comparing a population with a small cohort is inherently biased, as covariates, such as clinical status and baseline prognostic factors, are much more impactful in the small cohort.[31] To account for this bias, we used matched cohorts of equal size and bootstrapping to resample the data. The 1:1 comparison ensures covariates are equitably distributed, and the resampling increases the precision of our estimate of the hazard ratio and confidence interval. Using a matched population is also essential to control for confounding biases. Especially important was matching on lag time, whereby participants were only matched if their SEER counterpart survived at least as long as the lag time between diagnosis and enrolment in the study. This controls for immortal time bias. Immortal time is defined as a period where an event (mortality in this case) cannot occur. It is impossible for study participants to die during the time between diagnosis and enrolment; thus, it is important to compare them to registry patients who have survived at least as long. This is noticeable in our analysis, as both study participants and the population of matched SEER patients severely outperformed the global SEER population. This was almost certainly due to immortal time bias. Finally, the matched SEER Kaplan-Meier curves do not include all matched patients, rather, they include the lowest number of matches of all the study participants in the given group. Standardization to the least number of matches for each participant ensures that participants who could have a large number of matches do not skew the data. As previously mentioned, no statistical analyses were applied to these curves as they were solely intended to be a graphic representation of the data. Any statistical analysis would be inferior to what was generated using the matched bootstrap analysis.

The internal survival comparison was conducted using a time-varying covariate analysis. This type of analysis adjusts for the fact that covariates change during the follow-up period. Specifically, with regards to our study, there is a bias whereby the longer participants survive, the more likely they are to receive more treatments. This selection bias is accounted for and corrected in a time-varying covariate analysis. In our analysis, we compared participants who received at least one treatment with participants who received zero treatments, looking at the effect of the median number of treatments in each group. As an example, we saw a hazard ratio of 0.80 (20% reduction in risk of death) for participants receiving IVC in the breast cancer cohort. This means the hazard rate for a participant receiving 13 IVC treatments

would be 0.8 times the hazard rate for a participant receiving zero treatments. The median number of treatments was used as a comparator; however, using the statistical model, the hazard ratio can be adjusted for any number of treatments while keeping the same P value.

Limitations

This study has several important limitations. The use of SEER as a comparator is a limitation for several reasons. Firstly, SEER does not collect data on cases of cancer progression and thus does not capture patients with recurrent metastatic disease, rather only *de novo* cancer staging. This was partially controlled in our sub-analyses for participants diagnosed with *de novo* disease; however, this was a relatively small proportion of our population. Practical constraints prevented us from only enrolling patients with *de novo* stage IV disease due to the low incidence of initial stage IV diagnoses, particularly with breast cancer.[32] Secondly, there are inherent biases comparing population-level data with small cohorts as described above. This was at least partially controlled by our bootstrap analysis method. Thirdly, SEER does not gather data on Canadian patients; however, according to the American Cancer Society and Canadian Cancer Society, survival rates appear to be similar between Canada and the United States for all cancer types.[3,33] SEER also does not capture important confounders, such as smoking status, socioeconomic status, and conventional treatment regimens. Finally, data on the usage of TCIM therapies are also not present in SEER, which may introduce a dilutional confounding bias.

Another limitation is the lack of exclusion criteria based on date of diagnosis. Each enrolled participant had a lag time from diagnosis to enrolment, which if uncontrolled creates an immortal time bias. We addressed this bias by only including SEER matches who survived at least as long as the lag time between diagnosis and enrolment in study participants. However, this method does not eliminate all bias that results from lag time. For example, there may be reasons why someone seeks ND care long after their diagnosis, such as progression or increased symptom burden, which may negatively impact their survival outcomes. Another consequence of this lag time is that participants may have received different conventional treatments or were at different stages of treatment at the time of enrolment, which decreases the internal validity of the study. This lag time created another challenge given that the primary outcome was 5-year overall survival. Ten participants (2.7%) had a lag time longer than 5 years, which meant their follow-up time on the study was not included. Additionally, some participants had lag times between 24 and 60 months, which meant their follow-up time on the study was truncated. While 5-year survival is a common measure and truncating at 5 years helps reduce some of the bias of long-term survivors, it introduces new bias in that participant follow-up while on-study (i.e., when participants were potentially receiving naturopathic care) was removed. We attempted to control for this bias by including a sub-analysis of participants with shorter lag times.

There is likely selection bias from a few different sources. Firstly, there was no mechanism in place to ensure participants were screened and enrolled consecutively. Secondly, it is well documented that individuals with cancer who seek complementary healthcare services have more comprehensive insurance coverage, are more likely to be non-smokers, and have higher education and income,[34-36] all of which can affect clinical outcomes. Although these are general trends, we do not have specific data for our population.

Although some data were collected regarding conventional treatments received by study participants, the granularity of the data was not sufficient to assess whether participants adhered to standard oncologic care guidelines. Adherence to standard treatments would be expected to impact clinical outcomes.

Beyond limitations in study methodology, there are several other important considerations when interpreting these data. This study assessed 5-year survival as the primary outcome; however, likely not all participants sought naturopathic care to improve survival. Participants may have presented for side effect management or improving QOL but were included equally in the survival analysis. Data regarding adherence for most naturopathic therapies were not collected, and thus the degree to which participants followed the guidance provided by their ND is unknown. Furthermore, there are many participants who only saw their ND once. Therefore, it is important to recognize that the primary goal of the study was to assess whether at least one consultation with an ND, as delivered in real-world practice, affects survival. It does not assess the impact of consistent or optimal naturopathic care. While this could be considered a limitation, and valuable information can be gathered from assessing compliance, real-world research offers valuable insights into the typical outcomes expected in clinical practice.

The above limitations are difficult to address in an observational study. Given the challenges, it may not be appropriate to assess survival benefits by comparing a small cohort with registry data. It is clear from our analysis that using a matched population, especially the control of immortal time bias, is required at minimum. Additionally, enrolling patients shortly after diagnosis and limiting enrollment to those diagnosed *de novo* with the cancer stage under investigation would further mitigate potential bias. However, the lack of data regarding conventional treatment regimens and use of confounding treatments in SEER severely decreases internal validity, and selection bias will remain a concern. Ultimately, a clinical trial, whereby patients would be recruited in a hospital setting who are newly diagnosed and naïve to naturopathic care, would be the optimal way around these challenges. A trial of this nature is being conducted by a group in Ottawa, Canada, in which patients with newly diagnosed lung, gastric, or esophageal cancer are randomized to receive standard care plus naturopathic care or standard care alone.[37] However, studies of this magnitude are complex, costly, and suffer from reductions in external validity when using standardized treatment protocols.

Strengths

There are a few strengths worth noting. This is the first study to evaluate survival outcomes for patients with advanced cancer receiving naturopathic care, and thus the methods and findings are novel. Additionally, the multicentre and international recruitment increases the generalizability of our findings. The

prospective enrolment reduces selection bias. The statistical methods that were used for both the bootstrapped and time-varying covariate analysis helped reduce known biases with observational research. Lastly, the sub-analyses provide insights into the impact of important characteristics in our population and may be hypothesis-generating for future research.

CONCLUSION

This study demonstrated no survival advantages for patients with advanced breast, colorectal, pancreatic, or ovarian cancer who consulted with a naturopathic doctor compared with US registry data. Despite the lack of improvements, we cannot conclude that naturopathic medicine is ineffective for survival in this population due to the many biases and limitations in the study design which cannot be adequately controlled. This study is the first large-scale attempt to evaluate how consulting with a naturopathic doctor impacts cancer outcomes in a real-world setting. Further research in a more controlled setting, such as a clinical trial, is needed to clarify the role of naturopathic medicine for survival in people with advanced cancer.

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CONFLICTS OF INTEREST DISCLOSURE

We have read and understood the *CAND Journal*'s policy on conflicts of interest and declare that we have none.

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APPENDIX A: SEER SURVIVAL COMPARISON

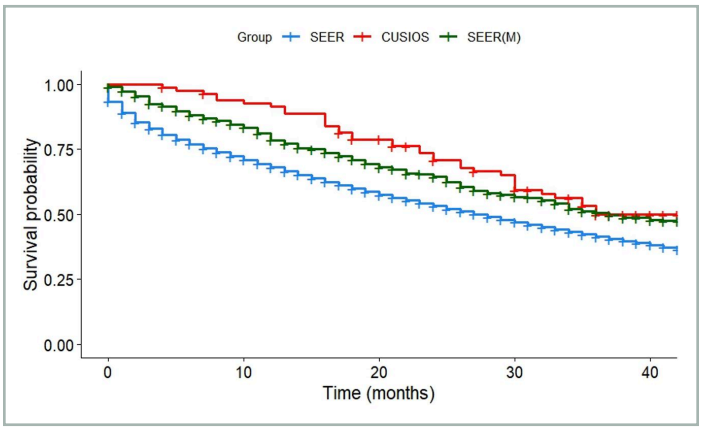

FIGURE A1 Breast cancer: survival of participants with lag time ≤ 6 months compared with SEER registry. SEER: All patients from SEER with Stage IV breast cancer (*N* = 35,551). SEER(M): Patients from SEER who matched with at least one study participant (*N* = 902). CUSIOS: Study population (*N* = 82). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results (registry data); CUSIOS: Canadian/US Integrative Oncology Study (study population).

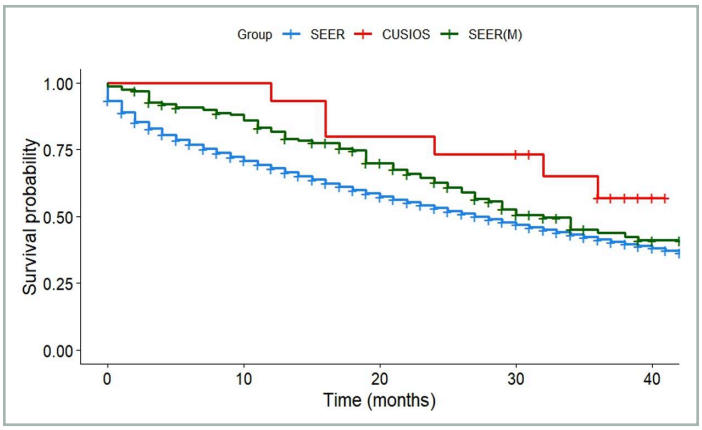

FIGURE A3 Breast cancer: survival of participants with *de novo* disease and lag time ≤ 6 months compared with SEER registry. SEER: All patients from SEER with Stage IV breast cancer (*N* = 35,551). SEER(M): Patients from SEER who matched with at least one study participant (*N* = 165). CUSIOS: Study population (*N* = 15). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results (registry data); CUSIOS: Canadian/US Integrative Oncology Study (study population).

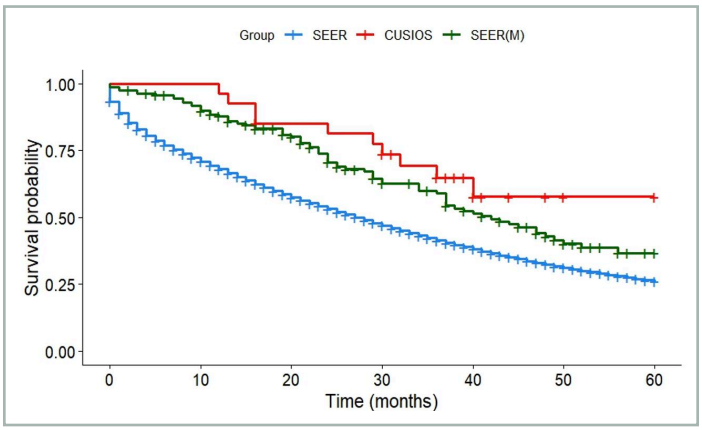

FIGURE A2 Breast cancer: survival of participants with *de novo* disease compared with SEER registry. SEER: All patients from SEER with Stage IV breast cancer (*N* = 35,551). SEER(M): Patients from SEER who matched with at least one study participant (*N* = 162). CUSIOS: Study population (*N* = 27). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results (registry data); CUSIOS: Canadian/US Integrative Oncology Study (study population).

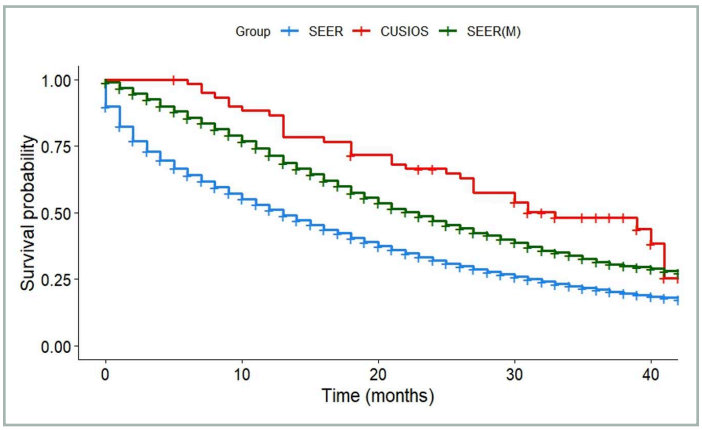

FIGURE A4 Colorectal cancer: survival of participants with lag time ≤ 6 months compared with SEER registry. SEER: All patients from SEER with Stage IV colorectal cancer (*N* = 71,735). SEER(M): Patients from SEER who matched with at least one study participant (*N* = 6,466). CUSIOS: Study population (*N* = 61). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results (registry data); CUSIOS: Canadian/US Integrative Oncology Study (study population).

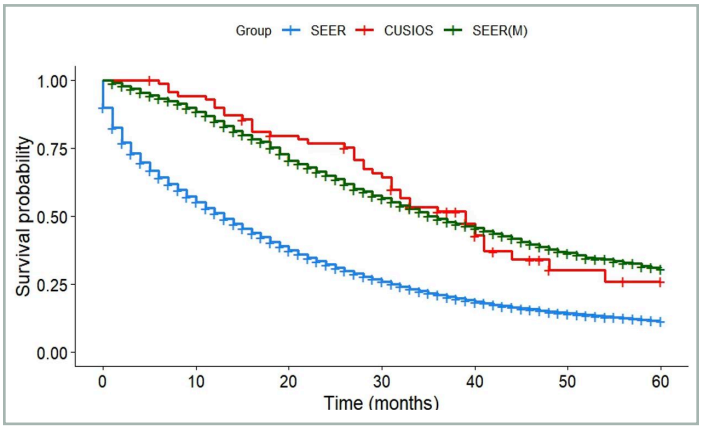

FIGURE A5 Colorectal cancer: survival of participants with *de novo* disease compared with SEER registry. SEER: All patients from SEER with Stage IV colorectal cancer (*N* = 71,735). SEER(M): Patients from SEER who matched with at least one study participant (*N* = 3,640). CUSIOS: Study population (*N* = 70). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results (registry data); CUSIOS: Canadian/US Integrative Oncology Study (study population).

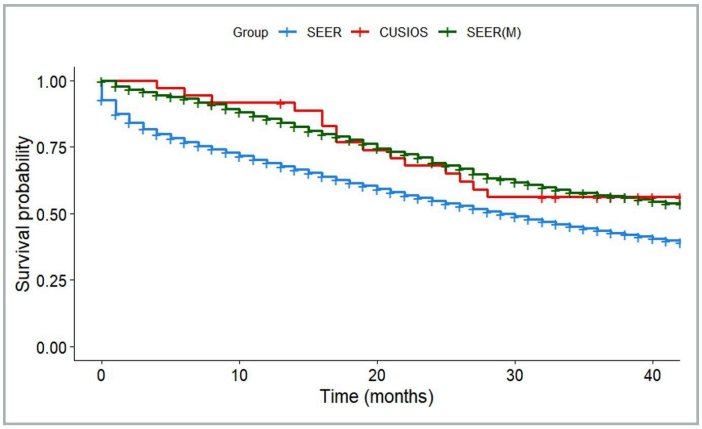

FIGURE A7 Ovarian cancer: survival of participants with lag time ≤ 8 months compared with SEER registry. SEER: All patients from SEER with Stage III or IV ovarian cancer (*N* = 32,847). SEER(M): Patients from SEER who matched with at least one study participant (*N* = 1,476). CUSIOS: Study population (*N* = 36). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results (registry data); CUSIOS: Canadian/US Integrative Oncology Study (study population).

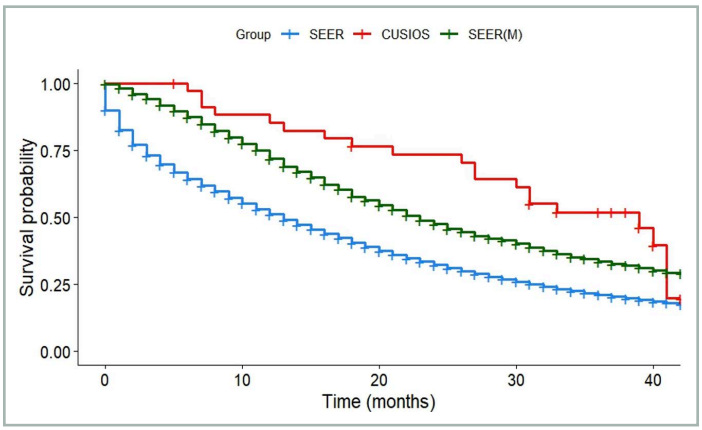

FIGURE A6 Colorectal cancer: survival of participants with *de novo* disease and lag time ≤ 6 months compared with SEER registry. SEER: All patients from SEER with Stage IV colorectal cancer (*N* = 71,735). SEER(M): Patients from SEER who matched with at least one study participant (*N* = 3,710). CUSIOS: Study population (*N* = 35). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results (registry data); CUSIOS: Canadian/US Integrative Oncology Study (study population).

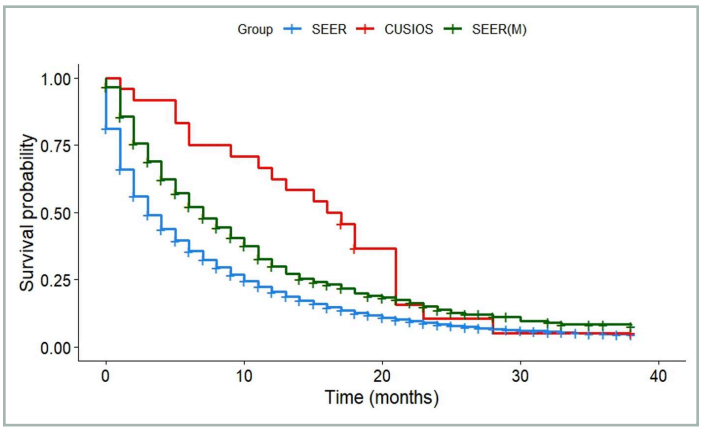

FIGURE A8 Pancreatic cancer: survival of participants with lag time ≤ 2 months compared with SEER registry. SEER: All patients from SEER with stage III or IV pancreatic cancer (*N* = 65,851). SEER(M): Patients from SEER who matched with at least one study participant (*N* = 624). CUSIOS: Study population (*N* = 24). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results (registry data); CUSIOS: Canadian/US Integrative Oncology Study (study population).

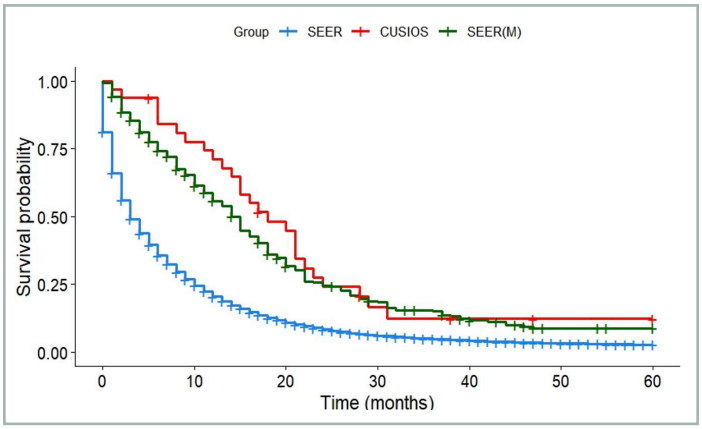

FIGURE A9 Pancreatic cancer: survival of participants with *de novo* disease compared with SEER registry. SEER: All patients from SEER with stage III or IV pancreatic cancer (*N* = 65,851). SEER(M): Patients from SEER who matched with at least one study participant (*N* = 384). CUSIOS: Study population (*N* = 32). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results (registry data); CUSIOS: Canadian/US Integrative Oncology Study (study population).

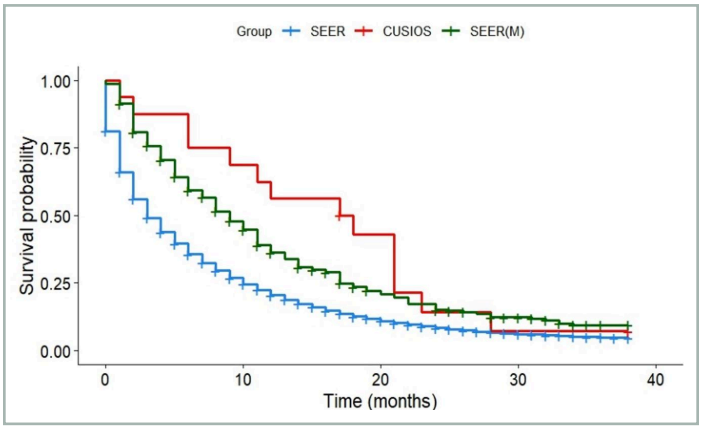

FIGURE A10 Pancreatic cancer: survival of participants with *de novo* disease and lag time ≤ 2 months compared with SEER registry. SEER: All patients from SEER with stage III or IV pancreatic cancer (*N* = 65,851). SEER(M): Patients from SEER who matched with at least one study participant (*N* = 416). CUSIOS: Study population (*N* = 16). This curve was created as a graphic representation to aid viewers in visualizing the data. Statistical analyses were only applied to the main bootstrapped analysis. SEER: Surveillance Epidemiology and End Results (registry data); CUSIOS: Canadian/US Integrative Oncology Study (study population).

APPENDIX B: INTERNAL SURVIVAL COMPARISON

TABLE A1 Survival Among Study Participants with Breast Cancer

Covariate	HR, 95% CI	P value
Univariate (single treatment)		
IV vitamin C	0.983 (0.969–0.997)	0.02
IV mistletoe	0.991 (0.973–1.010	0.38
Hyperthermia	0.993 (0.967–1.021)	0.64
ND visits	0.945 (0.896–0.997)	0.04
Age (continuous)	1.012 (0.993–1.032)	0.23
HR status (luminal A vs. HER2 enriched)	2.347 (0.568–9,693)	0.24
HR status (luminal B vs. HER2 enriched)	1.922 (0.320–11.530)	0.48
HR status (triple negative vs. HER2 enriched)	8.035 (1.763–36.609)	0.007
HR status (unknown vs. HER2 enriched)	1.701 (0.367–7.891)	0.50
Histology (lobular vs. ductal)	1.424 (0.764–2.653)	0.27
Histology (other vs. ductal)	0.626 (0.247–1.583)	0.32
Histology (unknown vs. ductal)	1.003 (0.539–1.864)	0.99
Multivariate (single treatment)		
IV vitamin C	0.967 (0.944–0.992)	0.01
IV mistletoe	1.031 (0.996–1.067)	0.08
Hyperthermia	1.008 (0.977–1.040)	0.63
ND visits	0.918 (0.861–0.980)	0.01
Age (continuous)	1.019 (0.997–1.041)	0.08
HR status (luminal A vs. HER2 enriched)	1.654 (0.384–7.107)	0.50
HR status (luminal B vs. HER2 enriched)	1.327 (0.213–8.266)	0.76
HR status (triple negative vs. HER2 enriched)	11.425 (2.330–56.033)	0.003
HR status (unknown vs. HER2 enriched)	1.283 (0.271–6.075)	0.75
Histology (lobular vs. ductal)	1.61 (0.805–3.218)	0.18
Histology (other vs. ductal)	0.701 (0.250–1.961)	0.50
Multivariate (median treatments)		
IV Vitamin C	0.651 (0.468–0.907)	0.01
IV mistletoe	1.69 (0.912–3.134)	0.08
Hyperthermia	1.096 (0.764–1.572)	0.63
ND visits	0.653 (0.473–0.903)	0.01

HR: Hormone Receptor. HER: Human Epidermal Growth Factor Receptor. IV: Intravenous. ND: Naturopathic Doctor

TABLE A2 Survival Among Study Participants with Colorectal Cancer

Covariate	HR, 95% CI	P value
Univariate (single treatment)		
IV vitamin C	0.996 (0.983–1,01)	0.58
IV mistletoe	0.993 (0.973–1.015)	0.53
Hyperthermia	0.996 (0.981–1.012)	0.60
ND visits	0.92 (0.859–0.984)	0.02
Age (continuous)	1.021 (0.999–1.044)	0.06
Sex (male vs. female)	1.272 (0.782–2.069)	0.33
Multivariate (single treatment)		
IV vitamin C	1.011 (0.983–1,040)	0.43
IV mistletoe	0.989 (0.960–1.020)	0.49
Hyperthermia	0.997 (0.971–1.024)	0.83
ND visits	0.898 (0.828–0.974)	0.009
Age (continuous)	1.02 (0.995–1.045)	0.12
Sex (male vs. female)	0.981 (0.579–1.663)	0.94
Multivariate (median treatments)		
IV vitamin C	1.154 (0.807–1.648)	0.43
IV mistletoe	0.871 (0.603–1.259)	0.49
Hyperthermia	0.956 (0.633–1.443)	0.83
ND visits	0.649 (0.471–0.895)	0.009

IV: Intravenous. ND: Naturopathic Doctor

TABLE A3 Survival Among Study Participants with Ovarian Cancer

Covariate	HR, 95% CI	P value
Univariate (single treatment)		
IV vitamin C	0.998 (0.981–1,02)	0.81
IV mistletoe	0.986 (0.945–1.027)	0.49
Hyperthermia	1.022 (0.993–1.053)	0.14
ND visits	0.974 (0.906–1.047)	0.47
Age (continuous)	1.017 (0.982–1.054)	0.34
Histology (serous vs. other)	0.794 (0.317–1.987)	0.62
Stage (III vs. IV)	1.979 (0.949–4.125)	0.07
Multivariate (single treatment)		
IV vitamin C	1.002 (0.970–1,036)	0.89
IV mistletoe	0.985 (0.930–1.043)	0.60
Hyperthermia	1.045 (1.001–1.091)	0.05
ND visits	0.934 (0.851–1.025)	0.15
Age (continuous)	1.034 (0.986–1.083)	0.17
Histology (serous vs. other)	0.828 (0.267–2.565)	0.74
Stage (III vs. IV)	1.803 (0.781–4.165)	0.17
Multivariate (median treatments)		
IV vitamin C	1.034 (0.587–1.823)	0.89
IV mistletoe	0.848 (0.454–1.584)	0.60
Hyperthermia	1.696 (1.011–2.845)	0.05
ND visits	0.712 (0.445–1.139)	0.15

IV: Intravenous. ND: Naturopathic Doctor

TABLE A4 Survival Among Study Participants with Pancreatic Cancer

Covariate	HR, 95% CI	P value
Univariate (single treatment)		
IV vitamin C	0.997 (0.980–1,015)	0.75
IV mistletoe	0.993 (0.954–1.032)	0.71
Hyperthermia	0.994 (0.973–1.016)	0.57
ND visits	0.882 (0.804–0.968)	0.008
Age (continuous)	1.011 (0.983–1.040)	0.44
Histology (adenocarcinoma vs. other)	0.729 (0.284–1.872)	0.51
Stage (III vs. IV)	1.32 (0.659–2.646)	0.43
Multivariate (single treatment)		
IV vitamin C	1.004 (0.964–1,046)	0.83
IV mistletoe	0.996 (0.948–1.046)	0.86
Hyperthermia	1.009 (0.959–1.062)	0.73
ND visits	0.87 (0.778–0.974)	0.02
Age (continuous)	1.007 (0.973–1.042)	0.68
Histology (adenocarcinoma vs. other)	0.77 (0.280–2.120)	0.61
Stage (III vs. IV)	1.299 (0.597–2.830)	0.51
Multivariate (median treatments)		
IV vitamin C	1.02 (0.830–1,253)	0.83
IV mistletoe	0.97 (0.672–1.401)	0.86
Hyperthermia	1.119 (0.592–2.116)	0.73
ND visits	0.499 (0.285–0.872)	0.02

IV: Intravenous. ND: Naturopathic Doctor

A Comprehensive Description of Naturopathic Care for Advanced Cancers: Outcomes from the Canadian/US Integrative Oncology Study

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ABSTRACT

Background: There is a paucity of real-world data on the treatments naturopathic doctors (NDs) use for supportive cancer care. We conducted an observational cohort study to comprehensively describe the treatments NDs with experience in cancer care recommend to their patients.

Methods: Patients with advanced breast, colorectal, ovarian, or pancreatic cancer were recruited from 12 North American naturopathic clinics and followed for 2 to 3 years. Therapeutic recommendations were abstracted from clinic records.

Results: 384 participants (154 breast, 112 colorectal, 71 ovarian, 47 pancreatic) were included in the analyses. The median number of ND visits was 5. The most common types of recommendations were natural health products (NHPs, 99% of participants), nutrition guidance (88%), and parenteral therapies (81%). Mental health (33%) and Traditional Chinese Medicine (29%) were least common. Participants were recommended a median of 11 NHPs throughout the study, with 430 unique products recommended across all participants. Nutrition guidance heavily favoured encouraging foods rather than discouraging them (83% vs. 17% of all dietary recommendations, respectively). Vitamin D, curcumin, intravenous vitamin C, increasing protein intake, and exercise were recommended to at least 50% of participants across each cancer type. Other common recommendations included melatonin, fish oil, *Trametes versicolor*, subcutaneous mistletoe, increasing vegetable intake, and eating behaviour changes. Recommendations were fairly uniform between cancer types, with the most variation seen in NHPs.

Conclusion: NDs frequently recommend NHPs, nutrition guidance, and parenteral therapies for people with advanced cancer. The diversity of unique recommendations suggests individualized care, yet some commonly used treatments demonstrate a degree of consistency.

Key Words Naturopathic medicine, integrative medicine, integrative oncology, naturopathic cancer care, supportive cancer care, naturopathic oncology, naturopathic treatments, treatment recommendations, naturopathic doctor, naturopathic physician, breast cancer, ovarian cancer, colorectal cancer, pancreatic cancer

INTRODUCTION

Traditional, complementary and integrative medicine (TCIM) is reported to be used by 40% to 80% of people with cancer.[1-3] Under the TCIM umbrella, naturopathic medicine (NM) is a system of care provided by naturopathic doctors (NDs) that includes the use of nutritional guidance, dietary supplements, herbal medicine, homeopathic remedies, intravenous and injection therapy, acupuncture, counselling and emotional support, and various lifestyle practices.[4] Naturopathic medicine is one of the most commonly practiced systems of TCIM in the Western world,[4] with approximately 8,000 licensed NDs in North America.[5] Studies suggest NM use is higher among those with cancer than the general population,[6] although the exact prevalence of use is unknown.

The goals of NM in cancer care include educating patients on adopting healthy lifestyles, managing side effects, improving

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treatment response, reducing recurrence risk, and optimizing overall health.[7] Although specialization within naturopathic medicine is not currently recognized by most state and provincial regulators, fellowship certification is established for cancer care through the American Board of Naturopathic Oncology, which is part of the Oncology Association of Naturopathic Physicians (OncANP).[8] Currently, 133 NDs across North America are Fellows of the American Board of Naturopathic Oncology, and about 400 NDs are members of the OncANP (email communication with OncANP Executive Director, Corey Murphy, March 6, 2025).

To date, clinical practice guidelines, which establish standard of care, are largely absent from NM. Limited guidelines for the broader field of integrative oncology have been published in recent years[9,10] but are not specific to naturopathic practice nor comprehensive enough to guide complex care. In 2019, the OncANP published a Principles of Care guidance document, which describes the naturopathic medical approach to cancer care.[7] The document provides guidance on how to deliver patient-centred care from diagnosis through to survivorship; however, it does not discuss treatments. The lack of standardization leads to limited knowledge of what recommendations NDs make for individuals with cancer. This is particularly relevant given the broad range of therapies available to NDs. To our knowledge, Standish et al. has published the only study reporting on naturopathic oncology care, which included patients with breast cancer of any stage.[11] Several surveys of NDs have also explored management for cancer;[12-14] however, survey responses may not accurately reflect real-world practice, and some data are likely outdated. Despite these contributions, gaps remain. Describing how NDs care for those with cancer enhances our understanding of the field, helps identify areas for improvement, improves transparency, and may aid the development of clinical practice guidelines and standards of care.

The Canadian/US Integrative Oncology Study is an observational cohort study with the overarching goal of studying naturopathic oncology in a real-world setting. The primary objective of the project was to measure survival in patients with advanced stage breast, colorectal, ovarian, or pancreatic cancer who consulted with an ND. Secondary objectives included describing the scope of treatments recommended to patients by NDs, comparing survival amongst enrolled participants based on the number of ND visits and the frequency of use of verifiably received naturopathic treatments, collecting health-related quality of life (QOL) data, estimating costs of cancer care, and gathering information on participants' qualitative experience of care.

In this paper, we describe the scope of therapeutic recommendations made by NDs to people with advanced breast, colorectal, ovarian, or pancreatic cancer. Survival, QOL, cost, and data on qualitative experiences will be reported in separate publications.

METHODS

This paper was written alongside our reports on survival, cost, QOL, and qualitative experiences. The study methods are similar across these publications; thus, there will be significant overlap.

Study Design

This was an observational study of patients with advanced stage breast, colorectal, ovarian, or pancreatic cancer who consulted with an ND at one of 12 clinics in North America. Recruitment and follow-up were prospective. Clinics were instructed to approach all eligible patients; however, we did not have a method to verify consecutive recruitment.

Setting

The study was conducted at 12 outpatient naturopathic clinics located in Canada (n = 5) and the US (n = 7). The primary coordinating centres were the Bastyr Center for Natural Health in Seattle, Washington, and The Centre for Health Innovation in Ottawa, Ontario. Additional sites were: Integrated Health Clinic Cancer Care Centre, Fort Langley, British Columbia; Marsden Centre for Excellence in Integrative Medicine, Vaughan, Ontario; Health Source Integrative Medical Centre, Kitchener, Ontario; Vital Victoria Naturopathic Clinic, Victoria, British Columbia; Naturopathic Specialists LLC, Scottsdale, Arizona; Salish Care Center, Fife, Washington; Hawaii Integrative Oncology, Kailua-Kona, Hawaii; Tree of Health Integrative Medicine, Woodinville, Washington; Seattle Integrative Cancer Center, Seattle, Washington; Advanced Integrative Medical Science Institute, Seattle, Washington. Clinics were selected for their focus in cancer care and NDs with a depth of experience in the field. A total of 29 NDs provided care to at least one study participant. All NDs had experience in a cancer care setting, and 15 were Fellows of the American Board of Naturopathic Oncology.

Participants

Eligible participants were adults 18 years of age and over who presented for care to a participating clinic with a confirmed diagnosis of one of the following:

- Metastatic breast cancer (*de novo* stage IV or recurrent)
- Metastatic colorectal cancer (*de novo* stage IV or recurrent)
- Advanced ovarian cancer (stage III or IV, *de novo* or recurrent)
- Advanced pancreatic cancer (stage III or IV, *de novo* or recurrent)

Stages were determined per the American Joint Committee on Cancer's staging guidelines (version 7). Participants additionally had to be citizens or permanent residents of the country in which they were receiving treatment. All participants signed an informed consent form in writing prior to participating. Recruitment began in June 2015 and concluded in March 2020. Participants were followed for at least 2 years and up to 3 years. Variable follow-up time occurred due to funding restraints, which arose due to a longer than anticipated recruitment period. All participants were offered a $200 stipend upon enrolment to be used towards any practitioner consultation at the participant's naturopathic clinic.

Regulatory Adherence

Ethics approval was obtained from the Research Ethics Board of the Canadian College of Naturopathic Medicine and the Institutional Review Board at the Office of Research Integrity at Bastyr University prior to study initiation. The study was registered with clinicaltrials.gov, NCT02494037.

Outcomes

The primary study outcome was to provide a comprehensive description of the type and frequency of naturopathic recommendations made to patients with advanced cancer. Only the incidence and frequency of these recommendations were recorded; compliance was not assessed.

Data Sources

Data were collected from naturopathic clinic records and hospital medical records. Naturopathic clinic records were reviewed from the first visit until the study end date, and conventional records were reviewed from diagnosis until the study end date.

Sample Size

The total expected study sample size was 400 patients, of which it was estimated 150 would have breast cancer, 150 would have colorectal cancer, 50 would have ovarian cancer, and 50 would have pancreatic cancer. The sample size was determined based on pragmatic considerations related to the number of estimated eligible patients the clinics would see, the expected rate of enrollment, study duration, and available funding.

Quantitative Variables

At each visit, all recommendations made by NDs were abstracted and separated into distinct categories using the Research Electronic Data Capture (REDCap) platform. Entries were verified by a second team member. Each recommendation was then placed into one of the following categories: natural health products (NHPs), nutrition, parenteral therapies, prescription and over-the-counter (OTC) medications, hyperthermia, Traditional Chinese Medicine (TCM) practices (e.g., acupuncture, moxibustion), physical medicine and body-based therapies (e.g., exercise, massage therapy, hydrotherapy), and mental health.

Nutrition recommendations were divided into encouragements and discouragements. Dietary encouragements encompassed recommendations to start, continue, or increase a specific food, type of food, or eating behaviour. Discouragements included recommendations to decrease, hold, or stop these items. A recommendation for a prescription or OTC medication included recommending an OTC medication (e.g., ibuprofen), writing a prescription for a medication (for practitioners with prescribing authority), or advising the patient to speak with a medical doctor or nurse practitioner about a medication. Cannabis was abstracted in the same manner given it is not considered an NHP in Canada. Hyperthermia recommendations encompassed both whole body and locoregional hyperthermia (LRHT). A recommendation was categorized as mental health support if it could conceivably help improve the participant's mental health and did not fit in any other recommendation category (e.g., recommendations to see a therapist, or to practice meditation).

In a companion paper reporting on the survival of our participants,[15] we included an analysis on survival time based on the number of intravenous vitamin C (IVC), IV mistletoe, and hyperthermia treatments. For this analysis, we collected the number of verifiably received IV and hyperthermia treatments. In this paper, we additionally report on the proportion of participants who started IV therapies and hyperthermia compared with those who were recommended those treatments.

Statistical Methods

Results were analyzed using frequency distributions and descriptive statistics. Standard deviation (SD) was used as a method of dispersion for mean values. Inter-quartile range (IQR) or range was used as a method of dispersion for median values. Items were included in the results if they were recommended to at least 10% of participants in at least one cancer type. The Chi-squared test and standardized residuals were used to analyze differences in recommendations between cancer types. Cramer's V was used to determine the strength of the association. Values ≤ 0.3 were considered weak, values between 0.3 and 0.5 were considered moderate, and values > 0.5 were considered strong. Standardized residuals above $|2.00|$ were considered significant. A significant positive residual (i.e., ≥ 2.00) indicates that a therapy or treatment was recommended more often than expected in that cancer type if it is assumed there is no difference between cancer types. A significant negative residual (i.e., ≤ -2.00) indicates a recommendation was made less often than expected. All results from the statistical analyses are presented in Appendix A, Tables A1–A10.

Data Availability Statement

Datasets used in this study are available by request only. Please contact Dugald Seely, dseely@thechi.ca, if you would like to request access to any datasets.

RESULTS

Participant Characteristics

In total, 400 patients were enrolled. Sixteen were deemed screen failures (i.e., ineligible after being enrolled), leaving 384 participants included in the analyses. One hundred fifty-four had breast cancer, 112 had colorectal cancer, 71 had ovarian cancer, and 47 had pancreatic cancer. Figure 1 shows participant flow throughout the study.

Mean age at enrolment was 57.3 ± 11.8 years. Fifty participants (36 ovarian, 14 pancreatic) had stage III disease upon enrolment; all other participants had metastatic disease. Of those with metastatic disease, 142 (43%) were diagnosed *de novo*. Eighty-eight percent of participants received conventional cancer treatments before the study period and 90% received treatments during the study period. Only 4 participants did not receive any conventional treatments. Table 1 shows participants' baseline clinical status and demographic characteristics separated by cancer type.

Naturopathic Consultations

The median number of ND visits across the study was 5 (IQR 3–8). This differed slightly by cancer type:

- Breast: median 6 (IQR 3–9)
- Colorectal: median 4 (IQR 2–7.5)
- Ovarian: median 5 (IQR 3–8)
- Pancreatic: median 4 (IQR 2–7)

Over time, participants across all cancer types had fewer ND consultations. For those who were still alive, 50% had a consultation in their second year on study and 43% had a consultation in their third year. For those who continued to see their ND, the number of visits also declined. The mean number of ND visits was 4.7 ± 3.2 in the first year, 2.9 ± 2.1 in the second year, and 2.4 ± 1.9 in the third year. Thirty-eight participants (10%) had only a single visit with their ND.

Recommendations – Overview

Natural health products, nutrition, and parenteral therapies were the most common treatment modalities, recommended to 99%, 88%, and 81% of all participants, respectively. Recommendations for mental health and TCM were made least often (33% and 29%, respectively). In general, the proportion of recommendations between cancer types was within 10% of others within the collective cohort. Notable exceptions include a higher incidence of hyperthermia recommendations in colorectal and pancreatic cancer, a higher incidence of prescription and OTC medications in pancreatic cancer, and a lower incidence of mental health and physical medicine recommendations in pancreatic cancer. Table 2 shows how frequently all modalities of naturopathic treatments were recommended to participants, separated by cancer type.

Recommendations – Natural Health Products

In total, there were 430 unique NHP recommendations across all participants. The median number of distinct recommendations per participant throughout the study was 11 (IQR 7–15). Approximately half (median = 6) of these recommendations were made at the initial consultation. Between cancer types, those with pancreatic cancer were recommended fewer NHPs (median = 7) compared with the other cancer types (breast: 12, colorectal: 10, ovarian: 12). There was a moderate positive correlation between the number of NHP recommendations and number of ND visits ($r = 0.57$, $p < 0.001$).

Table 3 shows the frequency of different categories of NHP recommendations. The most common items were vitamins and minerals (recommended to 93% of all participants), herbal medicine (83%), and hormone-based products (e.g., melatonin) (68%). Homeopathic remedies (18%), fibre supplements (6%), and essential oils (4%) were the least common.

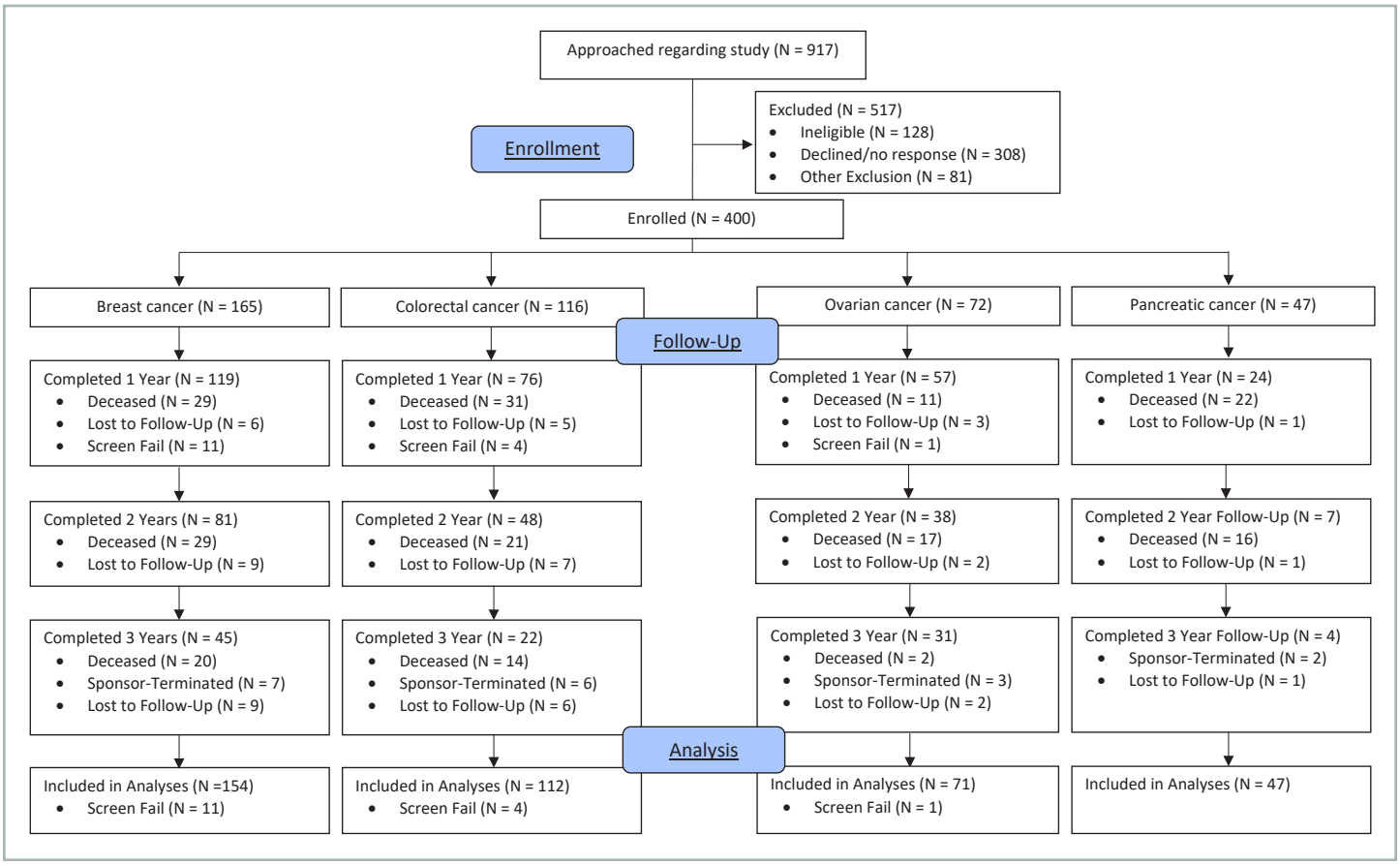

FIGURE 1 Participant Flow Diagram. Patients were only recorded as approached if an investigator believed they were eligible for the study and if the patient was interested in participating. Screen fail: patient was enrolled in the study but was later found to be ineligible.

Table 4 shows the frequency of specific NHP recommendations. The most common was vitamin D, made to 75% of participants. Only vitamin D and curcumin were recommended to at least 50% of participants across all cancer types. Other top recommendations included melatonin, *Trametes versicolor*, and omega-3 fatty acids, each recommended to at least 50% of the total population. A statistically significant Chi-squared test statistic was seen for 20 NHPs, indicating the distribution of recommendations was not uniform across all cancer types; however, all associations were weak (Cramer's V < 0.3). Several NHPs also showed statistically significant associations with one cancer type (i.e., a positive or negative residual). The breast cancer cohort had the most positive associations (n = 9 NHPs), indicating many treatments were recommended more frequently than expected for those with breast cancer. The pancreatic cancer cohort had the most negative associations (n = 4), indicating many treatments were recommended less frequently than expected for these participants.

Recommendations – Nutrition

Tables 5 and 6 show the most common nutrition encouragements and discouragements, respectively. Dietary encouragements were made much more often than discouragements (83% vs. 17% of all dietary recommendations, respectively). This trend was consistent across each cancer type. The top ten most encouraged dietary items were: protein-rich foods (e.g., poultry, fish, legumes), vegetables, eating behaviour changes and nutrition education, fruits, tea, nuts and seeds, fats, fasting (e.g., before chemotherapy, intermittent fasting), water, and whole grains. Protein-rich foods was the only recommendation made to at least 50% of participants across all cancer types. Tea recommendations were primarily green tea (63% of all tea recommendations) and herbal teas (36%) The most common eating behaviour recommendations were increasing caloric intake (23% of all recommendations) and eating small frequent meals (20%). The only items that were mainly discouraged

TABLE 1 Clinical Status and Demographics

Characteristic	Breast Cancer *n* (%)	Colorectal Cancer *n* (%)	Ovarian Cancer *n* (%)	Pancreatic Cancer *n* (%)	Total *n* (%)
Sex					
Male	0	50 (45)	0	23 (49)	73 (19)
Female	154 (100)	62 (55)	71 (100)	24 (51)	311 (81)
Cancer stage					
Stage III	N/A	N/A	36 (51)	14 (30)	50 (13)
Stage IV	100%	100%	35 (49)	33 (70)	334 (87)
ECOG performance status					
0, 1, 2	140 (91)	112 (100)	71 (100)	47 (100)	370 (96)
3, 4	14 (9)	0	0	0	14 (4)
Sites of metastasis[a,b]					
Liver	55 (36)	76 (68)	21 (29)	36 (77)	188 (49)
Bone	106 (69)	8 (7)	9 (12)	1 (3)	124 (36)
Lymph nodes	57 (37)	35 (31)	23 (32)	12 (26)	127 (33)
Lung	45 (29)	48 (43)	17 (24)	14 (29)	124 (32)
Brain	14 (9)	0	2 (3)	1 (3)	17 (5)
Number of sites of metastasis[b]					
1 site	51 (33)	39 (35)	29 (41)	22 (47)	141 (37)
2 sites	42 (27)	30 (27)	20 (29)	16 (34)	108 (28)
3 sites	25 (16)	24 (21)	11 (15)	6 (13)	66 (17)
4+ sites	36 (24)	19 (17)	11 (15)	3 (6)	69 (18)
Conventional treatments received during study period					
Chemotherapy	90 (58)	91 (81)	56 (79)	37 (79)	274 (71)
Monoclonal antibodies	67 (44)	70 (63)	24 (34)	3 (6)	164 (43)
Oral targeted therapy	75 (49)	15 (13)	20 (28)	3 (6)	113 (29)
Radiation therapy	53 (34)	27 (24)	10 (14)	11 (23)	101 (26)
Endocrine therapy	112 (73)	0 (0)	5 (7)	0 (0)	117 (30)
Surgery	14 (9)	24 (21)	20 (28)	3 (6)	61 (16)

Breast cancer: n = 154. Colorectal cancer: n = 112. Ovarian cancer: n = 71. Pancreatic cancer: n = 47. Total: n = 384.
[a] Not all sites of metastasis shown; multiple selections permitted.
[b] Only includes participants with metastatic disease. ECOG: Eastern Cooperative Oncology Group.

were sugar, refined grains, red meat, raw foods, and alcohol. One exception is in participants with pancreatic cancer, where red meat was encouraged slightly more often than it was discouraged (8% versus 6%, respectively). Teas (encouragement) and raw foods (discouragement) were the only items with significant non-uniformity across cancer types. Raw foods were discouraged more often than expected in participants with pancreatic cancer and less often than expected in participants with breast cancer.

Parenteral Therapies

Table 7 shows the most common parenteral therapies recommended to participants. Only 6 parenteral therapies were recommended to ≥ 10% of participants in at least one cancer type. These included IVC, IV and subcutaneous (SC) mistletoe, general nutrient infusions, and infusions of artesunate and dichloroacetate (DCA). IVC was by far the most common, recommended to at least 60% of participants across cancer types. Subcutaneous mistletoe was recommended to at least 40% of participants, and IV mistletoe was recommended to at least 30% of participants across cancer types. Dichloroacetate and artesunate were least common, both recommended to ≤ 10% of participants in total. No parenteral therapies showed significant non-uniformity between cancer types based on the Chi-squared test.

Other Notable Recommendations

Exercise was recommended to 57% of participants, with aerobic exercise (52%) being far more common than resistance training (18%). Cannabis and cannabinoids were recommended to 24%

TABLE 2 Recommendations by Treatment Modality

Recommendation Category	Breast Cancer *n* (%)	Colorectal Cancer *n* (%)	Ovarian Cancer *n* (%)	Pancreatic Cancer *n* (%)	Total *n* (%)
Natural health products	153 (99)	110 (98)	69 (97)	47 (100)	379 (99)
Nutrition guidance	136 (88)	96 (86)	65 (92)	40 (85)	337 (88)
Parenteral therapies	115 (75)	96 (86)	59 (83)	40 (85)	310 (81)
Physical medicine & body-based therapies	109 (71)	70 (62)	51 (72)	27 (57)	257 (70)
Prescription & OTC medications	78 (51)	46 (41)	37 (52)	28 (60)	189 (49)
Hyperthermia	46 (30)	54 (48)	21 (30)	23 (49)	144 (38)
Mental & emotional health guidance	54 (35)	37 (33)	26 (37)	11 (23)	128 (33)
Traditional Chinese Medicine	48 (31)	30 (27)	22 (31)	12 (26)	112 (29)

Breast cancer: *n* = 154. Colorectal cancer: *n* = 112. Ovarian cancer: *n* = 71. Pancreatic cancer: *n* = 47. Total: *n* = 384. This table only reports on recommendations; participants may or may not have used the recommended therapy. OTC: Over the counter.

TABLE 3 Natural Health Product Recommendations by Treatment Category

Category	Breast Cancer *n* (%)	Colorectal Cancer *n* (%)	Ovarian Cancer *n* (%)	Pancreatic Cancer *n* (%)	Total *n* (%)
Vitamins and minerals	145 (94)	104 (93)	67 (94)	42 (89)	358 (93)
Herbal medicine	125 (81)	95 (85)	62 (87)	35 (74)	317 (83)
Hormone-based product[a]	118 (77)	71 (63)	51 (72)	20 (43)	260 (68)
Medicinal mushrooms	111 (72)	64 (57)	42 (59)	19 (40)	236 (61)
Non-essential nutrients and phytochemicals	102 (66)	40 (36)	47 (66)	23 (49)	212 (55)
Proteins and amino acids	71 (46)	65 (58)	40 (56)	25 (53)	201 (52)
Essential fatty acids	72 (47)	55 (49)	41 (58)	25 (53)	193 (50)
Other natural products[b]	64 (42)	54 (48)	36 (51)	21 (45)	175 (46)
Probiotics	55 (36)	52 (46)	28 (39)	19 (40)	154 (40)
Functional foods[c]	69 (45)	25 (22)	26 (37)	13 (28)	133 (35)
Combination products[d]	48 (31)	23 (21)	23 (32)	13 (28)	107 (28)
Enzymes	33 (21)	26 (23)	11 (15)	20 (43)	90 (23)
Homeopathic remedies	40 (26)	14 (13)	11 (15)	5 (11)	70 (18)
Fibre supplements	10 (6)	4 (4)	2 (3)	6 (13)	22 (6)
Essential oils	7 (5)	5 (4)	3 (4)	2 (4)	17 (4)

Breast cancer: *n* = 154. Colorectal cancer: *n* = 112. Ovarian cancer: *n* = 71. Pancreatic cancer: *n* = 47. Total: *n* = 384. This table only reports on recommendations; participants may or may not have used the recommended therapy.
[a] Includes hormones that are classified as NHPs, namely melatonin and DHEA. This category does not include sex hormones.
[b] Includes NHPs which do not fit in another category. E.g., activated charcoal, gamma-aminobutyric acid, and modified citrus pectin.
[c] Includes foods which are used for purposes beyond usual nutritional value, such as flaxseed and medium-chain triglyceride oil.
[d] Includes products which contain two or more of the above categories (e.g., a product containing herbs and vitamins).
NHP = natural health product; DHEA = dehydroepiandrosterone.

of participants. Hydrotherapy and massage therapy were recommended to 19% and 11% of participants, respectively. Metformin (16%) and low-dose naltrexone (15%) were the most recommended prescription medications. Yoga and meditation/mindfulness were the most recommended activities to support mental health, each made to approximately 15% of participants. Acupuncture was recommended to 27% of participants. All prescription and OTC medications (except non-steroidal anti-inflammatory drugs), as well as hydrotherapy recommendations, were significantly different between cancer types per the Chi-squared test; however, associations were weak. Table 8 fully describes these recommendations.

TABLE 4 Natural Health Product Recommendations by Specific Product

Product	Breast Cancer *n* (%)	Colorectal Cancer *n* (%)	Ovarian Cancer *n* (%)	Pancreatic Cancer *n* (%)	Total *n* (%)
Vitamin D	121 (78)	83 (74)	55 (77)	30 (63)	289 (75)
Curcumin	104 (67)	73 (65)	51 (71)	32 (68)	260 (67)
Melatonin	118 (76)	71 (63)	51 (71)	**20 (42)**[b]	260 (67)
Trametes versicolor	97 (62)	55 (49)	36 (50)	**14 (29)**[b]	202 (52)
Omega 3 fatty acids	71 (46)	55 (49)	41 (57)	25 (53)	192 (50)
Probiotics	54 (35)	52 (46)	28 (39)	19 (40)	153 (39)
Magnesium	73 (47)	32 (28)	35 (49)	**8 (17)**[b]	148 (39)
B vitamins	59 (38)	33 (29)	34 (47)	15 (31)	141 (37)
L-glutamine	39 (25)	46 (41)	26 (36)	14 (29)	125 (32)
Vitamin C	**59 (38)**[a]	27 (24)	17 (24)	10 (21)	113 (29)
Linum usitatissimum	**62 (40)**[a]	**12 (10)**[b]	21 (29)	9 (19)	104 (27)
Multivitamin	45 (29)	26 (23)	18 (25)	10 (21)	99 (25)
Protein powder	26 (16)	28 (25)	16 (22)	13 (27)	83 (21)
Alpha-lipoic acid	26 (16)	16 (14)	20 (28)	**18 (38)**[a]	80 (20)
Enzymes	29 (18)	24 (21)	10 (14)	**17 (36)**[a]	80 (20)
Fermented wheat germ extract	**18 (11)**[b]	29 (25)	21 (29)	6 (12)	74 (19)
Coenzyme Q10	**44 (28)**[a]	**9 (8)**[b]	15 (21)	**1 (2)**[b]	69 (17)
Green tea extract	26 (16)	16 (14)	**22 (30)**[a]	4 (8)	68 (17)
Homeopathic remedies	**38 (24)**[a]	13 (11)	10 (14)	5 (10)	66 (17)
Zinc	23 (14)	21 (18)	12 (16)	8 (17)	64 (16)
Modified citrus pectin	24 (15)	13 (11)	12 (16)	6 (12)	55 (14)
Calcium	**33 (21)**[a]	9 (8)	11 (15)	2 (4)	55 (14)
Zingiber officinalis	**9 (5)**[b]	21 (18)	11 (15)	8 (17)	49 (12)
Berberine	24 (15)	8 (7)	14 (19)	3 (6)	49 (12)
Ganoderma lucidum	22 (14)	11 (9)	12 (16)	3 (6)	48 (12)
Silybum marianum	13 (8)	**24 (21)**[a]	6 (8)	4 (8)	47 (12)
Vitamin K	**33 (21)**[a]	7 (6)	3 (4)	2 (4)	45 (11)
Astragalus spp	17 (11)	8 (7)	13 (18)	6 (12)	44 (11)
Quercetin	19 (12)	10 (8)	8 (11)	3 (6)	40 (10)
Immune combination products[c]	21 (13)	10 (8)	1 (1)	3 (6)	35 (8)
Glycyrrhiza glabra	15 (9)	7 (6)	8 (11)	1 (2)	31 (8)
Boswellia serrata	**20 (12)**[a]	5 (4)	4 (5)	2 (4)	31 (8)
Withania somnifera	**21 (13)**[a]	4 (3)	5 (7)	1 (2)	31 (8)
Sesame oil	8 (5)	2 (1)	6 (8)	**7 (14)**[a]	23 (5)
Sulforaphane glucosinolate	16 (10)	0	5 (7)	0	21 (5)
Activated charcoal	0	9 (8)	0	5 (10)	14 (3)
Psyllium	5 (3)	2 (1)	2 (2)	**5 (10)**[a]	14 (3)

Breast cancer: $n = 154$. Colorectal cancer: $n = 112$. Ovarian cancer: $n = 71$. Pancreatic cancer: $n = 47$. Total: $n = 384$. This table only reports on recommendations; participants may or may not have used the recommended therapy.

[a] Significant positive residual from the Chi-squared test.

[b] Significant negative residual from the Chi-squared test.

[c] Encompasses various herbal formulas and combination products specifically labelled as immune support.

Treatments Received

Of the 144 participants who were recommended hyperthermia, 96 (67%) received treatments at one of the study clinics. Compared with the number of participants who were recommended IV therapies, 69% received one or more IVC infusions, 63% received IV mistletoe, 38% received general nutrient infusions, 14% received IV artesunate, and 4% received IV DCA.

DISCUSSION

In this multicentre North American observational study, we comprehensively described naturopathic treatment recommendations

TABLE 5 Dietary Encouragements

Product	Breast Cancer *n* (%)	Colorectal Cancer *n* (%)	Ovarian Cancer *n* (%)	Pancreatic Cancer *n* (%)	Total *n* (%)
Protein foods[a]	77 (50)	56 (50)	37 (52)	27 (57)	197 (51)
Vegetables	82 (53)	51 (45)	37 (52)	20 (42)	190 (49)
Eating behaviours and education	62 (40)	46 (41)	27 (38)	24 (51)	159 (41)
Teas	63 (40)	31 (27)	33 (46)	12 (25)	139 (36)
Fruits	49 (31)	45 (40)	30 (42)	14 (29)	138 (35)
Nuts and seeds	46 (29)	31 (27)	25 (35)	16 (34)	118 (30)
Fats	48 (31)	33 (29)	23 (32)	15 (31)	119 (30)
Fasting	51 (33)	27 (24)	22 (30)	8 (17)	108 (28)
Water	38 (24)	29 (25)	23 (32)	8 (17)	98 (25)
Whole grains	31 (20)	26 (23)	16 (22)	11 (23)	84 (21)
Specific diets	38 (24)	20 (17)	19 (26)	9 (19)	86 (22)
Fermented foods	32 (20)	21 (18)	23 (32)	6 (12)	82 (21)
Whole foods	26 (16)	29 (25)	16 (22)	7 (14)	78 (20)
Herbs/spices	29 (18)	24 (21)	13 (18)	7 (14)	73 (19)
Low glycemic index foods	26 (16)	22 (19)	16 (22)	5 (10)	69 (17)
Dairy	24 (15)	17 (15)	11 (15)	9 (19)	61 (15)
Fibre	19 (12)	18 (16)	12 (16)	7 (14)	56 (14)
Soups and broths	12 (7)	15 (13)	9 (12)	10 (21)	46 (11)
Alliums	11 (7)	15 (13)	8 (11)	5 (10)	39 (10)
Juice	17 (11)	9 (8)	7 (9)	6 (12)	39 (10)
Coffee	9 (5)	9 (8)	4 (5)	8 (17)	30 (7)
Red meat	8 (5)	13 (11)	7 (9)	4 (8)	32 (8)
Sugar substitute	7 (4)	10 (8)	10 (14)	3 (6)	30 (7)
Apple cider vinegar	8 (5)	4 (3)	8 (11)	2 (4)	22 (5)

Breast cancer: $n = 154$. Colorectal cancer: $n = 112$. Ovarian cancer: $n = 71$. Pancreatic cancer: $n = 47$. Total: $n = 384$. This table only reports on recommendations; participants may or may not have used the recommended therapy.
[a] Red meat was abstracted separately from protein foods.

TABLE 6: Dietary Discouragements

Product	Breast Cancer *n* (%)	Colorectal Cancer *n* (%)	Ovarian Cancer *n* (%)	Pancreatic Cancer *n* (%)	Total *n* (%)
Sugar	39 (25)	29 (26)	23 (32)	9 (19)	100 (26)
Refined grains	27 (18)	24 (21)	18 (25)	6 (13)	75 (20)
Red meat	21 (14)	19 (17)	16 (23)	3 (6)	59 (15)
Raw foods	**10 (6)**[b]	19 (17)	7 (10)	**12 (26)**[a]	48 (13)
Alcohol	9 (6)	9 (8)	9 (13)	2 (4)	29 (8)
Eating behaviours and education	8 (5)	7 (6)	8 (11)	2 (4)	25 (7)
Dairy	13 (8)	6 (5)	2 (3)	2 (4)	23 (6)

Breast cancer: $n = 154$. Colorectal cancer: $n = 112$. Ovarian cancer: $n = 71$. Pancreatic cancer: $n = 47$. Total: $n = 384$. This table only reports on recommendations; participants may or may not have used the recommended therapy.
[a] Significant positive residual from the Chi-squared test.
[b] Significant negative residual from the Chi-squared test.

for patients with late-stage breast, colorectal, ovarian, and pancreatic cancer. Participants were commonly recommended NHPs, IVC, and aerobic exercise, and received dietary counselling. Standish et al. previously provided a summary of naturopathic treatment recommendations for patients with any stage breast cancer.[11] Some data are consistent with our breast cancer cohort, including the high frequency of recommendations for vitamin D, curcumin, omega 3 fatty acids, and *Trametes versicolor*. Notably, dietary and exercise recommendations are much higher in both our breast cancer cohort and the entire study population. The reasons for these discrepancies are not clear. IV therapy recommendations were also significantly higher in our study; however, this is likely because only 12% of participants from Standish et al. had metastatic disease, which is where IVC has been most heavily studied.[16]

Our results demonstrate that naturopathic care for advanced cancer has some degree of consistency in the most common treatment recommendations while also offering a wide range of treatments. The consistency is demonstrated by the frequency with which certain NHPs, nutrition, and exercise interventions were recommended; vitamin D, curcumin, IVC, and aerobic exercise were all recommended to at least 50% of participants across all cancer types, with several other recommendations above 35%. This is notable given the large number of clinics involved in this study and the lack of practice guidelines in naturopathic cancer care. The individualized nature of care is evidenced by the wide array of unique treatment recommendations, with many having a low overall frequency of use. One possible explanation is the lack of practice guidelines which, given the large number of practitioners and locations of practice, could yield a variety of different treatments being used for similar conditions. However, this individuality is in line with principles of naturopathic medicine, namely, to treat the whole person and to identify the root cause of illness.[4] These principles emphasize a holistic and individualized approach to care that likely explains the broad scope of therapies recommended. Patients also seek TCIM care for a variety of reasons, such as improving cancer outcomes, side effect and symptom management, holistic care, general wellbeing, and management of other health conditions,[17] which results in more individualized and variable treatment.

TABLE 7 Parenteral Therapy Recommendations

Product	Breast Cancer *n* (%)	Colorectal Cancer *n* (%)	Ovarian Cancer *n* (%)	Pancreatic Cancer *n* (%)	Total *n* (%)
Vitamin C (intravenous)	96 (62)	76 (68)	51 (72)	34 (72)	257 (67)
Mistletoe (subcutaneous)	62 (40)	60 (54)	29 (41)	25 (53)	176 (46)
Mistletoe (intravenous)	47 (31)	41 (37)	25 (35)	22 (47)	135 (35)
General nutrients (intravenous)	11 (7)	15 (13)	7 (10)	9 (19)	42 (11)
Artesunate (intravenous)	19 (12)	8 (7)	6 (8)	3 (6)	36 (9)
Dichloroacetate (intravenous)	9 (6)	9 (8)	2 (3)	5 (11)	25 (7)

Breast cancer: $n = 154$. Colorectal cancer: $n = 112$. Ovarian cancer: $n = 71$. Pancreatic cancer: $n = 47$. Total: $n = 384$. This table only reports on recommendations; participants may or may not have used the recommended therapy. There were no significant positive or negative residuals from the Chi-squared test.

TABLE 8 Other Common Recommendations

Product	Breast Cancer *n* (%)	Colorectal Cancer *n* (%)	Ovarian Cancer *n* (%)	Pancreatic Cancer *n* (%)	Total *n* (%)
Exercise (aerobic)	82 (53)	56 (50)	40 (56)	23 (49)	201 (52)
Acupuncture	46 (30)	26 (23)	19 (27)	12 (26)	103 (27)
Cannabis and cannabinoids	42 (27)	24 (21)	15 (21)	14 (29)	95 (24)
Hydrotherapy	35 (23)	13 (12)	18 (25)	6 (13)	72 (19)
Exercise (resistance)	31 (20)	14 (13)	15 (21)	10 (21)	70 (18)
Metformin	28 (18)	7 (6)	**21 (30)**[a]	6 (13)	62 (16)
Yoga	25 (16)	16 (14)	13 (18)	4 (9)	58 (15)
Meditation and/or mindfulness	19 (12)	20 (18)	11 (15)	2 (4)	52 (14)
Low dose naltrexone	25 (16)	**8 (7)**[b]	11 (15)	12 (26)	56 (13)
Massage therapy	19 (12)	8 (7)	13 (18)	3 (6)	43 (11)
Acetyl salicylic acid	20 (13)	**2 (2)**[b]	8 (11)	3 (6)	33 (9)
NSAIDs	11 (7)	14 (12)	3 (4)	4 (9)	32 (8)
Dichloroacetate (oral)	4 (3)	**12 (11)**[a]	3 (4)	4 (9)	23 (6)

Breast cancer: $n = 154$. Colorectal cancer: $n = 112$. Ovarian cancer: $n = 71$. Pancreatic cancer: $n = 47$. Total: $n = 384$. This table only reports on recommendations; participants may or may not have used the recommended therapy. NSAID: Non-steroidal anti-inflammatory drug.
[a] Significant positive residual from the Chi-squared test.
[b] Significant negative residual from the Chi-squared test.

In general, most treatments were recommended uniformly between the four cancer types. There are several reasons this consistency between cancer types may exist. Firstly, many patients seek TCIM care for symptom management and general wellbeing, where treatments may be less dependent on cancer type. These treatments may target an underlying physiological process independent of cancer type, such as malnutrition, cachexia/sarcopenia, nausea, or immune function. Secondly, some treatments have demonstrated benefit across a variety of cancer types. For example, exercise improves QOL and symptom management across various advanced cancers,[18] and many NHPs, such as vitamin D,[19] *Trametes versicolor*,[20] and melatonin,[21] have demonstrated benefit for cancer outcomes among various cancers. Finally, some natural products have a large body of preclinical evidence demonstrating activity against diverse targets of cancer growth and metastasis which are common among various cancer types, such as curcumin[22,23] and green tea extract.[24,25] In this scenario, if safety has been established in humans and limited clinical data are available, it is possible such treatments may be recommended across cancer types.

Although there were no strong associations between any treatments and cancer type, more than 50% of the NHPs analyzed showed statistically significant non-uniformity between cancer types. This suggests there may be some specificity in the care provided by NDs in this domain. For some of the differences found in NHP recommendations, there are reasonable justifications. Participants with pancreatic cancer had a smaller overall number of NHP recommendations compared with other cancer types and the most significant negative residuals. This may be due to the higher incidence of digestive issues, cachexia, and sarcopenia,[26] which could result in NDs recommending fewer oral supplements to avoid worsening digestion or decreasing food intake. *Linum usitatissimum* (flaxseed) recommendations were higher in breast cancer (and to a lesser degree ovarian cancer), likely due to the lignan content, which impacts estrogen metabolism and signaling.[27-31] Digestive enzymes were more frequently recommended in pancreatic cancer, which is almost certainly due to the high incidence of exocrine pancreatic insufficiency and digestive upset in this population.[32] Calcium and vitamin K were more common in those with breast cancer, which could be due to a higher rate of osteoporosis and fractures in this cohort.[33] However, for other discrepancies, the reasons are not clear, and in most cases the differences may not be clinically meaningful.

Natural health products were the most common treatment modality used by NDs. While we cannot know the reasons why a specific NHP or category of NHPs was recommended, the frequency of use of certain products is likely dependent on a variety of factors, including patient concerns and preferences, available evidence, potential for pleiotropic effects, clinician experience, and feasibility. For example, many of the top recommendations, including vitamin D, curcumin, melatonin, omega 3 fatty acids, and *Trametes versicolor*, have evidence for improving a variety of outcomes in both cancer and non-cancer populations, which could explain their high frequency of use. Vitamin D has been shown to reduce cancer mortality,[19] decrease opioid use and fatigue in a palliative cancer setting,[34] and reduce depressive symptoms.[35,36] Curcumin has been shown to improve QOL,[36] reduce inflammation,[36] and help treat a wide variety of cancer treatment-related side effects.[37,38] Melatonin has some evidence for improved survival,[21] but ample evidence to improve sleep.[39] Omega 3 fatty acids can help maintain lean body mass and overall nutrition status[40,41] and may prevent oxaliplatin-induced peripheral neuropathy.[42] *Trametes versicolor* has evidence for improved survival and immunomodulatory effects.[20,43-45] These NHPs have the potential to benefit many patients; thus, it is not surprising they were the most recommended. It is notable that the evidence for NHP use in cancer care is more robust for symptom and side effect management than cancer survival outcomes. Therefore, it is reasonable to think that NHPs are used more often for these outcomes. This is strengthened by the fact that the number of ND visits significantly correlated with the number of NHP recommendations, which aligns with NDs addressing new side effects or adapting their treatment plans to complement different conventional cancer treatments.

Dietary counselling was the second most common treatment modality and the most uniform across all cancer types. The most notable finding is the overwhelming number of dietary encouragements compared with discouragements. Emphasizing the benefits of certain foods instead of the harms of others (e.g., encouraging whole foods rather than discouraging processed foods) promotes a "gain-framed" approach, which is more effective when trying to elicit a behaviour change.[46] Research has also shown that people who set approach-oriented goals are more likely to succeed than people who set avoidance-related goals.[47] Additionally, people with advanced cancer are at a greater risk for malnutrition, cachexia, and sarcopenia;[48,49] thus, an emphasis on restricting foods may be detrimental.

Many of the top dietary encouragements, namely protein foods, vegetables, eating behaviour changes and nutrition education, and fruits (Table 5), could represent a combination of the most important and/or the most deficient aspects of nutrition for people with cancer. Research has shown that, for those with cancer, protein intakes of less than 1.2 g/kg are associated with muscle wasting and intakes above 1.4 g/kg are associated with muscle maintenance.[50] This is significantly higher than the recommended daily allowance for adults (approximately 0.8 g/kg)[51] and thus supports the recommendation to increase protein intake. Data also indicate that neither Americans nor Canadians consume the recommended daily intakes for fruits and vegetables;[52,53] thus, recommendations to increase consumption are in line with this finding. Additionally, Canadians and Americans are generally deficient in fibre,[54,55] which could also contribute to the high incidence of vegetable and fruit recommendations. Naturopathic doctors also discussed eating behaviours and nutrition education with many participants. Given that NDs focus on encouragements, and adding foods to the diet has been shown to be more difficult than removing them,[56] emphasizing eating behaviours and providing education can help develop a better relationship with food, which could help participants adopt dietary changes.[57] Beyond these top recommendations, others were used more sparingly. This could be due to patient overwhelm. Research shows that focusing on a few dietary changes at a time improves the likelihood of patient

compliance.[56] Furthermore, given the unique nutritional needs and preferences of each person, it is reasonable to expect that nutrition guidance may be more varied between patients.

The top dietary discouragements, including added sugars, refined grains, red meat, and alcohol, are in line with the World Cancer Research Fund's guidelines for cancer prevention.[58] Raw foods were also heavily discouraged, likely to ease digestion for patients undergoing cancer treatments. In addition to the absolute number of discouraged foods being lower than those encouraged, these specific discouragements are not high in frequency compared with those most encouraged. While positive framing partially explains this, practitioners are also likely to only record dietary recommendations if a change is perceived as needed, especially for discouragements like reduced alcohol intake.

Recommendations for mental health, TCM, and hyperthermia were among the least common (Table 2). The low incidence of recommendations for TCM and hyperthermia is not surprising. Hyperthermia is only offered at a limited number of participating clinics, which decreases the likelihood that patients have access to this therapy. Although many studies support the use of TCM practices in patients with cancer, such as acupuncture, the strongest evidence is for the treatment of certain cancer-related symptoms[9] that may not be experienced by all patients. Furthermore, not all NDs practice acupuncture or other TCM practices. The low incidence of mental health recommendations is unexpected given the holistic nature of naturopathic medicine, the wide variety of items included in this category, and the importance of mental health, especially in people with cancer. Research has shown that people with cancer are at an increased risk for mental health disorders and reduced general mental wellbeing.[59-62] Mental health is a complex subject and defining what is or is not a recommendation to support mental health is difficult. For example, certain aspects of nutrition and exercise could also serve as mental health support but were not categorized as mental health recommendations in this study. Furthermore, it is well documented that there are often errors in chart notes, including discrepancies between what is documented versus what is discussed during an appointment.[63-65] One qualitative study showed that, during 10 physician visits, social and emotional topics were discussed in each visit yet only documented 30% of the time.[66] Discussion amongst the clinician-investigators related to this topic revealed that, at least among some practitioners, this aspect of care is often talked about with patients but not always charted. The lack of mental health recommendations we observed could indicate a practice gap in ND care, either due to a lack of discussion surrounding mental health or due to a lack of effective documentation.

A recent survey of NDs who provide supportive cancer care collected data on the self-reported frequency of use of different treatment modalities.[14] A section of this survey asked NDs how often they "frequently" recommend or refer out for certain therapies. This presents a unique opportunity to compare NDs' perception of their care and the documented frequencies of recommendations from chart notes. Although a rigorous comparison is not possible, given what NDs perceive as "frequent" is subjective and the survey was not restricted to late-stage cancers, some general correlations can be made. Of the 99 respondents in the survey, 95% reported they frequently discussed nutrition and nutritional supplements, 63% reported they frequently recommended exercise, 46% reported they frequently recommended acupuncture or TCM, and 39% reported they frequently recommended OTC medications. This aligns with the data we collected on how often these items are recommended in practice. Two items contradict our data. First, 45% of NDs reported they frequently recommended IV and infusion therapy; however, over 80% of our cohort were recommended these therapies. This is almost certainly due to differences in patient populations; IV therapies are likely recommended far less frequently to patients with early stage or curative cancers, which would decrease the overall frequency of these recommendations in a survey that did not distinguish between cancer stages. Secondly, 72% of NDs reported they frequently recommended mind–body therapies, and 63% reported they frequently recommended or referred out for mental health counselling, whereas only 33% of our cohort were given recommendations pertaining to their mental health. This strengthens our hypothesis that there may be a gap in what is discussed versus what is documented, or it suggests that NDs do not discuss mental health as often as they believe.

Strengths and Limitations

To our knowledge, this is the largest study which comprehensively describes naturopathic treatment recommendations to patients with advanced cancers. The amount of data collected is novel in this field and the documentation we present describes the diverse and comprehensive nature of naturopathic oncology care across North America.

One prominent limitation was our ability to effectively categorize and summarize the data we collected. Firstly, clinical judgment was required from study clinician-investigators for most recommendations. For example, many NHPs are commercial or combination products, and clinical judgment was used to categorize these as separate compounds or a single product. Secondly, the intent of the treating ND when making a recommendation was not known, which can make categorizing treatments difficult. For example, if a recommendation was made to eat more fish, it was not clear whether the goal was to increase omega 3 intake, increase protein, or decrease intake of other forms of animal-protein. Finally, some items, such as yoga therapy, conceivably fit into multiple categories (i.e., mental health and exercise).

Other limitations include variations in licensure, scope of practice, and access to equipment between provinces and states, which inherently reduces the overall incidence of many recommendations such as IV therapies, prescription drugs, and hyperthermia. Additionally, data regarding adherence for these therapies were not collected, and thus the degree to which participants followed the guidance provided by their ND is unknown. Finally, since we did not capture the intention behind the use of each recommendation, our ability to interpret the findings is limited.

CONCLUSION

This observational study provides a comprehensive overview of naturopathic treatment recommendations for patients with

late-stage breast, colorectal, ovarian, and pancreatic cancers in North America. Naturopathic doctors recommend a diverse array of treatments, highlighting the individualized nature of naturopathic care. Despite the large variety of treatments overall, the frequency with which several interventions are used is notable, suggesting some degree of consistency of care. Furthermore, there were no treatments recommended for one cancer type appreciably more than all others; however, minor differences were demonstrated, particularly with NHPs. Frequently, patients are recommended several NHPs, including vitamins, minerals, and herbal medicines. Intravenous vitamin C is commonly recommended, most patients are encouraged to exercise, and naturopathic doctors routinely give nutrition counselling using a positive framing approach that emphasizes the encouragement of certain foods and eating behaviours over discouragement. Mental health recommendations were low across all cancer types, which could indicate a practice gap or documentation issue. The data presented offer insights into the types of treatments used by naturopathic doctors and their consistency of use across different cancer types. These findings will enhance patients' and healthcare providers' understanding of the care provided by naturopathic doctors and inform future research avenues.

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CONFLICTS OF INTEREST DISCLOSURE

We have read and understood the *CAND Journal*'s policy on conflicts of interest and declare that we have none.

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APPENDIX A: STATISTICAL ANALYSES

TABLE A1 Chi-Squared Analyses for Natural Health Product Recommendations

Product	Breast Cancer *n* (%)	Colorectal Cancer *n* (%)	Ovarian Cancer *n* (%)	Pancreatic Cancer *n* (%)	Chi-squared statistic	P value	Cramer's V
Vitamin D	121 (78)	83 (74)	55 (77)	30 (63)	4.47	0.21	0.11
Curcumin	104 (67)	73 (65)	51 (71)	32 (68)	0.88	0.83	0.05
Melatonin	118 (76)	71 (63)	51 (71)	20 (42)	20.71	< 0.001	0.23
Trametes versicolor	97 (62)	55 (49)	36 (50)	14 (29)	17.13	0.001	0.21
Omega 3 fatty acids	71 (46)	55 (49)	41 (57)	25 (53)	2.87	0.41	0.09
Probiotics	54 (35)	52 (46)	28 (39)	19 (40)	3.50	0.32	0.10
Magnesium	73 (47)	32 (28)	35 (49)	8 (17)	21.78	< 0.001	0.24
B vitamins	59 (38)	33 (29)	34 (47)	15 (31)	6.88	0.08	0.13
L-glutamine	39 (25)	46 (41)	26 (36)	14 (29)	8.06	0.04	0.14
Vitamin C	59 (38)	27 (24)	17 (24)	10 (21)	11.46	0.009	0.17
Linum usitatissimum	62 (40)	12 (10)	21 (29)	9 (19)	30.46	< 0.001	0.28
Multivitamin	45 (29)	26 (23)	18 (25)	10 (21)	2.16	0.54	0.07
Protein powder	26 (16)	28 (25)	16 (22)	13 (27)	3.84	0.28	0.10
Alpha-lipoic acid	26 (16)	16 (14)	20 (28)	18 (38)	15.38	0.002	0.20
Enzymes	29 (18)	24 (21)	10 (14)	17 (36)	9.06	0.03	0.15
Fermented wheat germ extract	18 (11)	29 (25)	21 (29)	6 (12)	14.97	0.002	0.20
Coenzyme Q10	44 (28)	9 (8)	15 (21)	1 (2)	27.72	< 0.001	0.27
Green tea extract	26 (16)	16 (14)	22 (30)	4 (8)	12.29	0.006	0.18
Homeopathic remedies	38 (24)	13 (11)	10 (14)	5 (10)	10.41	0.02	0.16
Zinc	23 (14)	21 (18)	12 (16)	8 (17)	0.69	0.88	0.04
Modified citrus pectin	24 (15)	13 (11)	12 (16)	6 (12)	1.35	0.71	0.06
Calcium	33 (21)	9 (8)	11 (15)	2 (4)	13.91	0.003	0.19
Zingiber officinalis	9 (5)	21 (18)	11 (15)	8 (17)	11.47	0.009	0.17
Berberine	24 (15)	8 (7)	14 (19)	3 (6)	9.08	0.03	0.15
Ganoderma lucidum	22 (14)	11 (9)	12 (16)	3 (6)	4.05	0.26	0.10
Silybum marianum	13 (8)	24 (21)	6 (8)	4 (8)	12.43	0.006	0.18
Vitamin K	33 (21)	7 (6)	3 (4)	2 (4)	23.66	< 0.001	0.25
Astragalus Spp	17 (11)	8 (7)	13 (18)	6 (12)	5.45	0.14	0.12
Quercetin	19 (12)	10 (8)	8 (11)	3 (6)	1.75	0.63	0.07
Immune combination products[1]	21 (13)	10 (8)	1 (1)	3 (6)	11.62	0.009	0.17
Glycyrrhiza glabra	15 (9)	7 (6)	8 (11)	1 (2)	4.29	0.23	0.11
Boswellia serrata	20 (12)	5 (4)	4 (5)	2 (4)	8.47	0.04	0.15
Withania somnifera	21 (13)	4 (3)	5 (7)	1 (2)	11.82	0.008	0.18
Sesame oil	8 (5)	2 (1)	6 (8)	7 (14)	11.49	0.009	0.17
Sulforaphane glucosinolate	16 (10)	0	5 (7)	0	N/A	N/A	N/A
Activated charcoal	0	9 (8)	0	5 (10)	N/A	N/A	N/A
Psyllium	5 (3)	2 (1)	2 (2)	5 (10)	7.85	0.05	0.14

Breast cancer: $n = 154$. Colorectal cancer: $n = 112$. Ovarian cancer: $n = 71$. Pancreatic cancer: $n = 47$.

TABLE A2 Standardized Residuals for Natural Health Product Recommendations

Product	Standardized Residuals			
	Breast Cancer (Recommended, Not Recommended)	Colorectal Cancer (Recommended, Not Recommended)	Ovarian Cancer (Recommended, Not Recommended)	Pancreatic Cancer (Recommended, Not Recommended)
Vitamin D	0.474, -0.826	-0.141, 0.245	0.214, -0.373	-0.903, 1.576
Curcumin	-0.027, 0.038	-0.325, 0.471	0.422, -0.611	0.031, -0.045
Melatonin	1.345, -1.947	-0.555, 0.804	0.422, -0.611	-2.096, 3.035
Trametes versicolor	1.777, -1.872	-0.51, 0.538	-0.221, 0.233	-2.157, 2.272
Omega 3 fatty acids	-0.684, 0.684	-0.134, 0.134	0.923, -0.923	0.309, -0.309
Probiotics	-0.94, 0.765	1.104, -0.898	-0.054, 0.044	0.063, -0.051
Magnesium	1.699, -1.338	-1.661, 1.308	1.5, -1.181	-2.356, 1.855
B vitamins	0.247, -0.187	-1.226, 0.929	1.595, -1.208	-0.516, 0.391
L-glutamine	-1.572, 1.092	1.58, -1.098	0.601, -0.417	-0.332, 0.231
Vitamin C	2.171, -1.384	-0.945, 0.602	-0.998, 0.637	-1.244, 0.793
Linum usitatissimum	3.142, -1.915	-3.329, 2.029	0.404, -0.246	-1.045, 0.637
Multivitamin	0.909, -0.532	-0.67, 0.392	-0.028, 0.016	-0.576, 0.337
Protein powder	-1.263, 0.663	0.771, -0.405	0.167, -0.088	0.891, -0.468
Alpha-lipoic acid	-1.074, 0.551	-1.518, 0.779	1.354, -0.695	2.623, -1.346
Enzymes	-0.544, 0.279	0.138, -0.071	-1.246, 0.639	2.304, -1.182
Fermented wheat germ extract	-2.144, 1.047	1.596, -0.78	1.978, -0.967	-1.016, 0.496
Coenzyme Q10	3.104, -1.453	-2.48, 1.161	0.628, -0.294	-2.562, 1.199
Green tea extract	-0.243, 0.113	-0.861, 0.399	2.659, -1.233	-1.498, 0.695
Homeopathic remedies	2.241, -1.021	-1.425, 0.649	-0.631, 0.287	-1.083, 0.493
Zinc	-0.526, 0.235	0.54, -0.242	0.048, -0.022	0.06, -0.027
Modified citrus pectin	0.414, -0.169	-0.759, 0.311	0.574, -0.235	-0.282, 0.115
Calcium	2.33, -0.953	-1.758, 0.719	0.261, -0.107	-1.824, 0.746
Zingiber officinalis	-2.403, 0.919	1.774, -0.679	0.645, -0.247	0.818, -0.313
Berberine	0.981, -0.375	-1.664, 0.637	1.641, -0.628	-1.224, 0.468
Ganoderma lucidum	0.627, -0.237	-0.802, 0.303	1.049, -0.396	-1.186, 0.448
Silybum marianum	-1.347, 0.503	2.78, -1.038	-0.913, 0.341	-0.731, 0.273
Vitamin K	3.52, -1.282	-1.691, 0.616	-1.844, 0.672	-1.495, 0.545
Astragalus Spp	-0.154, 0.055	-1.349, 0.485	1.706, -0.614	0.265, -0.095
Quercetin	0.739, -0.252	-0.488, 0.166	0.222, -0.076	-0.857, 0.292
Immune combination products[1]	1.994, -0.622	0.026, -0.008	-2.507, 0.781	-0.569, 0.177
Glycyrrhiza glabra	0.728, -0.216	-0.679, 0.201	0.947, -0.281	-1.435, 0.425
Boswellia serrata	2.146, -0.636	-1.344, 0.398	-0.723, 0.214	-0.921, 0.273
Withania somnifera	2.43, -0.72	-1.677, 0.497	-0.306, 0.091	-1.435, 0.425
Sesame oil	-0.40, 0.10	-1.82, 0.46	0.85, -0.21	2.49, -0.63
Sulforaphane glucosinolate	N/A	N/A	N/A	N/A
Activated charcoal	N/A	N/A	N/A	N/A
Psyllium	-0.26, 0.05	-1.03, 0.20	-0.37, 0.07	2.51, -0.49

TABLE A3 Chi-Squared Analyses for Nutrition Encouragement Recommendations

Product	Breast Cancer *n* (%)	Colorectal Cancer *n* (%)	Ovarian Cancer *n* (%)	Pancreatic Cancer *n* (%)	Chi-squared statistic	P value	Cramer's V
Protein foods[1]	77 (50)	56 (50)	37 (52)	27 (57)	0.91	0.82	0.05
Vegetables	82 (53)	51 (45)	37 (52)	20 (42)	2.67	0.46	0.08
Eating behaviours and education	62 (40)	46 (41)	27 (38)	24 (51)	2.23	0.53	0.08
Teas	63 (40)	31 (27)	33 (46)	12 (25)	10.56	0.01	0.17
Fruits	49 (31)	45 (40)	30 (42)	14 (29)	4.01	0.26	0.10
Nuts and seeds	46 (29)	31 (27)	25 (35)	16 (34)	1.46	0.69	0.06
Fats	48 (31)	33 (29)	23 (32)	15 (31)	0.21	0.98	0.02
Fasting	51 (33)	27 (24)	22 (30)	8 (17)	5.95	0.11	0.12
Water	38 (24)	29 (25)	23 (32)	8 (17)	3.62	0.31	0.10
Whole grains	31 (20)	26 (23)	16 (22)	11 (23)	0.47	0.92	0.04
Specific diets	38 (24)	20 (17)	19 (26)	9 (19)	2.85	0.42	0.09
Fermented foods	32 (20)	21 (18)	23 (32)	6 (12)	7.70	0.05	0.14
Whole foods	26 (16)	29 (25)	16 (22)	7 (14)	4.34	0.23	0.11
Herbs/spices	29 (18)	24 (21)	13 (18)	7 (14)	0.97	0.81	0.05
Low glycemic index foods	26 (16)	22 (19)	16 (22)	5 (10)	3.05	0.38	0.09
Dairy	24 (15)	17 (15)	11 (15)	9 (19)	0.44	0.93	0.03
Fibre	19 (12)	18 (16)	12 (16)	7 (14)	1.13	0.77	0.05
Soups and broths	12 (7)	15 (13)	9 (12)	10 (21)	6.66	0.08	0.13
Alliums	11 (7)	15 (13)	8 (11)	5 (10)	2.93	0.40	0.09
Juice	17 (11)	9 (8)	7 (9)	6 (12)	1.04	0.79	0.05
Coffee	9 (5)	9 (8)	4 (5)	8 (17)	6.84	0.08	0.13
Red meat	8 (5)	13 (11)	7 (9)	4 (8)	3.78	0.29	0.10
Sugar substitute	7 (4)	10 (8)	10 (14)	3 (6)	6.49	0.09	0.13
Apple cider vinegar	8 (5)	4 (3)	8 (11)	2 (4)	5.27	0.15	0.12

Breast cancer: $n = 154$. Colorectal cancer: $n = 112$. Ovarian cancer: $n = 71$. Pancreatic cancer: $n = 47$. 1: Red meat included as a separate recommendation.

TABLE A4 Standardized Residuals for Nutrition Encouragement Recommendations

Product	Standardized Residuals			
	Breast Cancer (Recommended, Not Recommended)	Colorectal Cancer (Recommended, Not Recommended)	Ovarian Cancer (Recommended, Not Recommended)	Pancreatic Cancer (Recommended, Not Recommended)
Protein foods[1]	-0.226, 0.232	-0.192, 0.197	0.095, -0.098	0.588, -0.604
Vegetables	0.665, -0.658	-0.593, 0.587	0.315, -0.312	-0.675, 0.668
Eating behaviours and education	-0.221, 0.186	-0.055, 0.046	-0.442, 0.372	1.029, -0.865
Teas	0.972, -0.732	-1.499, 1.129	1.44, -1.085	-1.215, 0.915
Fruits	-0.853, 0.639	0.749, -0.561	0.888, -0.665	-0.703, 0.527
Nuts and seeds	-0.192, 0.128	-0.582, 0.388	0.681, -0.454	0.41, -0.273
Fats	0.04, -0.027	-0.29, 0.194	0.213, -0.142	0.114, -0.076
Fasting	1.168, -0.731	-0.802, 0.502	0.455, -0.284	-1.435, 0.898
Water	-0.208, 0.122	0.078, -0.046	1.146, -0.671	-1.153, 0.675
Whole grains	-0.463, 0.245	0.303, -0.16	0.119, -0.063	0.224, -0.119
Specific diets	0.598, -0.321	-1.015, 0.545	0.777, -0.417	-0.47, 0.253
Fermented foods	-0.154, 0.08	-0.596, 0.311	2.013, -1.049	-1.274, 0.664
Whole foods	-0.944, 0.477	1.31, -0.662	0.416, -0.21	-0.824, 0.416
Herbs/spices	-0.051, 0.025	0.587, -0.284	-0.135, 0.066	-0.647, 0.314
Low glycemic index foods	-0.318, 0.149	0.418, -0.196	0.908, -0.425	-1.186, 0.555
Dairy	-0.094, 0.041	-0.188, 0.082	-0.083, 0.036	0.561, -0.244
Fibre	-0.73, 0.302	0.412, -0.17	0.511, -0.211	0.056, -0.023
Soups and broths	-1.501, 0.554	0.432, -0.159	0.17, -0.063	1.842, -0.679
Alliums	-1.173, 0.395	1.075, -0.361	0.294, -0.099	0.104, -0.035
Juice	0.344, -0.116	-0.704, 0.237	-0.079, 0.026	0.561, -0.189
Coffee	-0.874, 0.254	0.085, -0.025	-0.657, 0.191	2.259, -0.658
Red meat	-1.349, 0.407	1.2, -0.362	0.445, -0.134	0.042, -0.013
Sugar substitute	-1.451, 0.422	0.423, -0.123	1.891, -0.55	-0.351, 0.102
Apple cider vinegar	-0.280, 0.070	-0.950, 0.240	1.950, -0.480	-0.420, 0.100

[1] Red meat included as a separate recommendation.

TABLE A5 Chi-Squared Analyses for Nutrition Discouragement Recommendations

Product	Breast Cancer *n* (%)	Colorectal Cancer *n* (%)	Ovarian Cancer *n* (%)	Pancreatic Cancer *n* (%)	Chi-squared statistic	P value	Cramer's V
Sugar	39 (25)	29 (26)	23 (32)	9 (19)	2.69	0.44	0.08
Refined grains	27 (18)	24 (21)	18 (25)	6 (13)	3.55	0.31	0.10
Red meat	21 (14)	19 (17)	16 (23)	3 (6)	6.3	0.10	0.13
Raw foods	10 (6)	19 (17)	7 (10)	12 (26)	14.87	0.002	0.20
Alcohol	9 (6)	9 (8)	9 (13)	2 (4)	4.08	0.25	0.10
Eating behaviours and education	8 (5)	7 (6)	8 (11)	2 (4)	3.48	0.32	0.10

Breast cancer: $n = 154$. Colorectal cancer: $n = 112$. Ovarian cancer: $n = 71$. Pancreatic cancer: $n = 47$.

TABLE A6 Standardized Residuals for Nutrition Discouragement Recommendations

Product	Standardized Residuals			
	Breast Cancer (Recommended, Not Recommended)	Colorectal Cancer (Recommended, Not Recommended)	Ovarian Cancer (Recommended, Not Recommended)	Pancreatic Cancer (Recommended, Not Recommended)
Sugar	-0.174, 0.103	-0.031, 0.018	1.049, -0.622	-0.926, 0.549
Refined grains	-0.561, 0.277	0.454, -0.224	1.11, -0.547	-1.049, 0.517
Red meat	-0.547, 0.233	0.432, -0.184	1.541, -0.657	-1.571, 0.669
Raw foods	-2.108, 0.797	1.336, -0.505	-0.629, 0.238	2.527, -0.955
Alcohol	-0.771, 0.22	0.186, -0.053	1.571, -0.449	-0.822, 0.235
Eating behaviours and education	-0.64, 0.169	-0.108, 0.029	1.571, -0.415	-0.606, 0.16

TABLE A7 Chi-Squared Analyses for Parenteral Recommendations

Product	Breast Cancer *n* (%)	Colorectal Cancer *n* (%)	Ovarian Cancer *n* (%)	Pancreatic Cancer *n* (%)	Chi-squared statistic	P value	Cramer's V
Vitamin C (intravenous)	96 (62)	76 (68)	51 (72)	34 (72)	2.90	0.41	0.09
Mistletoe (subcutaneous)	62 (40)	60 (54)	29 (41)	25 (53)	6.36	0.10	0.13
Mistletoe (intravenous)	47 (31)	41 (37)	25 (35)	22 (47)	4.36	0.23	0.11
General nutrients (intravenous)	11 (7)	15 (13)	7 (10)	9 (19)	6.31	0.10	0.13
Artesunate (intravenous)	19 (12)	8 (7)	6 (8)	3 (6)	2.81	0.42	0.09
Dichloroacetate (intravenous)	9 (6)	9 (8)	2 (3)	5 (11)	3.45	0.33	0.09

Breast cancer: $n = 154$. Colorectal cancer: $n = 112$. Ovarian cancer: $n = 71$. Pancreatic cancer: $n = 47$.

TABLE A8 Standardized Residuals for Parenteral Recommendations

Product	Standardized Residuals			
	Breast Cancer (Recommended, Not Recommended)	Colorectal Cancer (Recommended, Not Recommended)	Ovarian Cancer (Recommended, Not Recommended)	Pancreatic Cancer (Recommended, Not Recommended)
Vitamin C (intravenous)	-0.696, 0.99	0.12, -0.171	0.505, -0.719	0.454, -0.645
Mistletoe (subcutaneous)	-1.022, 0.94	1.21, -1.113	-0.621, 0.571	0.745, -0.685
Mistletoe (intravenous)	-0.97, 0.715	0.259, -0.191	0.008, -0.006	1.347, -0.992
General nutrients (intravenous)	-1.424, 0.499	0.786, -0.275	-0.275, 0.096	1.702, -0.597
Artesunate (intravenous)	1.201, -0.386	-0.772, 0.248	-0.254, 0.082	-0.67, 0.215
Dichloroacetate (intravenous)	-0.324, 0.086	0.633, -0.167	-1.22, 0.322	1.109, -0.293

TABLE A9 Chi-Squared Analyses for Other Common Recommendations

Product	Breast Cancer *n* (%)	Colorectal Cancer *n* (%)	Ovarian Cancer *n* (%)	Pancreatic Cancer *n* (%)	Chi-squared statistic	P value	Cramer's V
Exercise (aerobic)	82 (53)	56 (50)	40 (56)	23 (49)	0.97	0.81	0.05
Acupuncture	46 (30)	26 (23)	19 (27)	12 (26)	1.51	0.68	0.06
Cannabis and cannabinoids	42 (27)	24 (21)	15 (21)	14 (29)	2.33	0.51	0.08
Hydrotherapy	35 (23)	13 (12)	18 (25)	6 (13)	8.49	0.04	0.15
Exercise (resistance)	31 (20)	14 (13)	15 (21)	10 (21)	3.53	0.32	0.1
Metformin	28 (18)	7 (6)	21 (30)	6 (13)	18.43	< 0.001	0.22
Yoga	25 (16)	16 (14)	13 (18)	4 (9)	2.37	0.50	0.08
Meditation and/or mindfulness	19 (12)	20 (18)	11 (15)	2 (4)	5.66	0.13	0.12
Low dose naltrexone	25 (16)	8 (7)	11 (15)	12 (26)	9.88	0.02	0.16
Massage therapy	19 (12)	8 (7)	13 (18)	3 (6)	6.76	0.08	0.13
Acetyl salicylic acid	20 (13)	2 (2)	8 (11)	3 (6)	11.33	0.01	0.17
NSAIDs	11 (7)	14 (12)	3 (4)	4 (9)	4.4	0.22	0.11
Dichloroacetate	4 (3)	12 (11)	3 (4)	4 (9)	8.51	0.04	0.15

Breast cancer: $n = 154$. Colorectal cancer: $n = 112$. Ovarian cancer: $n = 71$. Pancreatic cancer: $n = 47$.

TABLE A10 Standardized Residuals for Other Common Recommendations

Product	Standardized Residuals			
	Breast Cancer (Recommended, Not Recommended)	Colorectal Cancer (Recommended, Not Recommended)	Ovarian Cancer (Recommended, Not Recommended)	Pancreatic Cancer (Recommended, Not Recommended)
Exercise (aerobic)	0.155, -0.162	-0.343, 0.359	0.465, -0.488	-0.323, 0.338
Acupuncture	0.73, -0.442	-0.737, 0.446	-0.01, 0.006	-0.171, 0.103
Cannabis and cannabinoids	0.632, -0.362	-0.704, 0.404	-0.612, 0.351	0.696, -0.399
Hydrotherapy	1.14, -0.548	-1.746, 0.839	1.285, -0.617	-0.947, 0.455
Exercise (resistance)	0.552, -0.261	-1.42, 0.671	0.572, -0.27	0.489, -0.231
Metformin	0.629, -0.276	-2.606, 1.144	2.817, -1.236	-0.577, 0.253
Yoga	0.361, -0.152	-0.223, 0.094	0.695, -0.293	-1.163, 0.491
Meditation and/or mindfulness	-0.406, 0.161	1.241, -0.491	0.447, -0.177	-1.73, 0.685
Low dose naltrexone	0.536, -0.222	-2.062, 0.852	0.201, -0.083	1.966, -0.812
Massage therapy	0.423, -0.15	-1.282, 0.455	1.791, -0.636	-0.986, 0.35
Acetyl salicylic acid	1.86, -0.57	-2.458, 0.754	0.769, -0.236	-0.517, 0.159
NSAIDs	-0.512, 0.154	1.528, -0.461	-1.199, 0.362	0.042, -0.013
Dichloroacetate	-1.72, 0.434	2.043, -0.516	-0.607, 0.153	0.706, -0.178

The Role of Naturopathic Medicine During Active Surveillance in Prostate Cancer

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ABSTRACT

Background: Active surveillance (AS) is increasingly used in low-risk prostate cancer, presenting an opportunity for integrative interventions to delay progression and improve overall health. This review explores the role of diet, exercise, and nutritional supplements in AS.

Methods: A narrative review of clinical and observational studies on dietary patterns, physical activity (PA), and nutritional supplements in AS and pre-surgical prostate cancer research.

Results: Plant-based and Mediterranean diets may reduce Gleason-grade progression, though randomized controlled trials (RCTs) show mixed results. Exercise, particularly high-intensity interval training (HIIT), may influence prostate-specific antigen (PSA) kinetics. Nutritional supplements such as vitamin D, green tea polyphenols, lycopene, mushroom mycelium extract, glucoraphanin, and fish oil show potential but inconsistent effects. Cardiovascular disease mortality surpasses prostate cancer mortality in men with localized disease, underscoring the need for cardiometabolic support alongside AS. Multimodal approaches integrating diet, exercise, and supplementation may offer the greatest benefit.

Conclusion: While no single intervention is proven to prevent prostate cancer progression, a comprehensive, personalized approach, including diet, exercise, and additional integrative therapies, may optimize outcomes in motivated patients. Future research should focus on evaluating multimodal integrative strategies in AS.

Key Words Integrative oncology, lifestyle medicine, complementary therapies, nutritional supplements, plant-based diet, exercise, Mediterranean diet, naturopathic oncology

INTRODUCTION

Prostate cancer is the most common cancer among Canadian men, with an estimated 1 in 7 receiving a diagnosis in their lifetime.[1] Often slow-growing, prostate cancer has one of the highest 5-year survival rates of all cancers in Canada (95%). Increasing recognition that low-risk prostate cancer carries minimal mortality risk has led to the widespread adoption of active surveillance (AS) as a standard management strategy.[2] Unlike watchful waiting, which focuses on symptom management, AS involves routine monitoring for signs of disease progression, with the intent to initiate curative treatment if necessary.[3] This strategy aims to preserve quality of life while reducing the morbidity associated with definitive therapy.[4]

The Canadian Urological Association recommends AS as the preferred strategy for patients with low-risk, localized prostate cancer characterized by a Gleason score of 6 or below and a prostate-specific antigen (PSA) level of less than 10 ng/mL.[5] This approach may also be considered for select patients with low-volume, localized prostate cancer with a Gleason score of 3 + 4 = 7. Surveillance protocols typically include PSA testing every 3 to 6 months, digital rectal examination annually, and a confirmatory biopsy within 6 to 12 months, followed by repeat biopsies every 3 to 5 years. However, there is a trend towards fewer biopsies with the increased use of multiparametric magnetic resonance imaging (MRI).[6] Reclassification to a higher-risk category occurs if the Gleason score increases to 7 or above or if there is a significant rise in tumour volume. Long-term AS studies indicate that clinical progression and the need for definitive treatment initiation occur in 45% to 57% of patients within 15 years.[7,8]

Active surveillance offers a valuable window for patients to adopt evidence-based, noninvasive strategies aimed at slowing disease progression and potentially delaying or preventing the need for invasive treatments that often compromise quality of life. Despite the growing adoption of AS as a primary management strategy for low-risk prostate cancer, there is limited consensus on

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the most effective complementary approaches to support patients during this period.[2] Given the prolonged monitoring involved in AS for prostate cancer,[7,8] long-term health strategies such as diet modification,[12-18] exercise,[19-21] and targeted nutritional supplements may be able to offer significant clinical benefits.[22-30] There is increasing evidence suggesting that these interventions may modulate tumour biology and slow the progression of prostate cancer.

Naturopathic oncology is a subfield of naturopathic medicine that applies naturopathic principles to cancer care,[9] with the Oncology Association of Naturopathic Physicians advancing the field since 2004.[10] Approximately 56% of men with prostate cancer use complementary and integrative medicine, with nutritional supplements being the most common modality.[11] Naturopathic oncology providers integrate clinical trial data, traditional use, and patient preferences to offer evidence-based recommendations aimed at managing treatment side effects, optimizing treatment response, preventing recurrence, and enhancing overall well-being.[10] With their training in dietary and lifestyle interventions, along with individualized supplement recommendations, naturopathic doctors are well positioned to support motivated prostate cancer patients in integrating safe, evidence-based complementary therapies into AS.

This review will examine current research exploring how naturopathic approaches can support patients with prostate cancer during AS, with the goal of prolonging the time before active treatment becomes necessary. By synthesizing the available evidence, we aim to equip naturopathic doctors with practical insights for integrating these strategies into clinical practice.

NATURAL INTERVENTIONS DURING ACTIVE SURVEILLANCE

Dietary Changes

Several observational studies have investigated the role of diet quality in men undergoing AS, primarily using dietary indices such as the Healthy Eating Index (HEI), the Alternative Mediterranean Diet, the Dietary Approaches to Stop Hypertension (DASH), and plant-based diet indices (PDI). These studies provide insight into potential dietary patterns that may influence disease progression.

Three studies evaluated the impact of HEI scores on prostate cancer progression. Gregg et al. (2019) analyzed HEI scores in 411 men over a median follow-up of 3 years and observed no statistically significant differences in progression rates.[12] In contrast, a larger 2024 prospective cohort study by Su et al. followed 886 men over 6.5 years and reported that higher baseline HEI and energy-adjusted HEI scores were significantly associated with a lower risk of grade reclassification, suggesting that longer follow-up may be necessary to detect meaningful effects of dietary interventions.[13] However, Schenk et al. assessed diet quality in 546 men based on adherence to HEI as well as Alternative Mediterranean Diet, and DASH scores, finding no significant association with Gleason grade progression over a median follow-up of 7.8 years.[14]

Other studies have examined the impact of the Mediterranean and plant-based dietary patterns. Gregg et al. (2021) investigated the Mediterranean diet in 410 men over 3 years, noting an inverse relationship between adherence and Gleason grade progression; however, it did not reach statistical significance.[15] More recently, Liu et al. followed 2,602 men for 6.5 years and assessed diet quality using the PDI and healthful-PDI. While healthful-PDI scores were not significantly linked to progression risk, higher PDI scores were associated with a 47% reduced risk of disease progression (ptrend = 0.003).[16] Notably, among 680 men with Gleason grade ≥ 7, higher healthful-PDI adherence correlated with a 55% lower progression risk (ptrend = 0.01), indicating that dietary patterns may have varying effects based on baseline risk factors.

Other observational studies have explored dietary patterns using alternative scoring systems. Vandersluis et al. categorized foods as either prostate cancer-promoting (e.g., dairy, fast food, red meat) or protective (e.g., fish, tomato products, cruciferous vegetables, soy, berries, and red wine).[17] Data from 237 men was retrospectively evaluated; however, no significant differences in dietary intake scores were observed between men who experienced disease progression and those who did not.

While observational research provides valuable insights, randomized controlled trials (RCT) are needed to establish causality. However, RCT evidence in this area remains limited. One RCT by Parsons et al. enrolled 478 men with low-risk prostate cancer and randomized them to either a telephone-based behavioural counselling intervention, promoting at least seven daily servings of vegetables or a control group receiving written dietary information.[18] After 2 years, 245 progression events were recorded, with no significant differences between groups, raising questions about the effectiveness of dietary interventions in modifying short-term disease outcomes.

Observational studies suggest that adherence to dietary patterns emphasizing plant-based foods, the Mediterranean diet, and overall diet quality may be associated with a reduced risk of prostate cancer progression in men on AS.[12-17] However, findings remain inconsistent, and longer follow-up appears necessary to detect meaningful effects. While RCT evidence remains limited, the null findings from the Parsons et al. trial highlight the challenges of dietary intervention studies, including adherence, follow-up duration, and potential differences in baseline dietary patterns.[18] Future research is needed to clarify the role of dietary modifications in delaying prostate cancer progression and identify the most impactful nutritional strategies for patients on AS.

Exercise Interventions

Observational studies have explored the relationship between physical activity (PA) and prostate cancer progression, with mixed findings regarding its impact on disease outcomes.

Three retrospective studies have assessed PA levels in men undergoing AS. Papadopoulos et al. examined time to AS discontinuation in 421 patients, 107 of whom initiated active treatment over a median follow-up of 2.5 years.[19] No significant association was found between PA levels and AS duration. Similarly, Vandersluis et al. analyzed PA levels in two cohorts and found no statistically significant difference in PA between those with stable disease and those who progressed.[17] However, a more recent 2021 study by Brassetti et al. followed 85 men for a median of

3 years and found that those who experienced disease progression were less physically active ($p = 0.056$).[20] The risk of prostate cancer reclassification differed significantly among the three PA groups (sedentary, moderately active, and active; $p = 0.033$), with the highest risk observed in the sedentary group. Although some studies suggest a protective effect of higher activity levels, findings remain inconsistent, again highlighting the need for larger, long-term studies when assessing lifestyle interventions.

Despite the growing body of observational evidence, RCTs investigating the effects of exercise on disease progression during AS are scarce. To date, only one RCT has assessed the direct impact of exercise in this setting.[21]

Kang et al. randomized 52 men with prostate cancer on AS to either a high-intensity interval training (HIIT) program or usual care.[21] The HIIT group participated in a 12-week, thrice-weekly supervised exercise program, with intensity tailored to baseline cardiopulmonary fitness. The usual care group was advised to maintain their typical activity levels. Compared with the usual care group, the HIIT group experienced statistically significant reductions in PSA levels, PSA velocity, and prostate cancer cell growth.

While observational studies suggest that higher PA levels may be associated with a lower risk of prostate cancer progression, findings are mixed, and prospective studies directly examining this relationship in patients undergoing AS are needed.[17,19-20] The only RCT conducted to date suggests that structured, supervised exercise, particularly HIIT, may decrease PSA levels and tumour cell growth.[21] However, additional large-scale, long-term trials are needed to confirm these findings and determine the optimal exercise regimen for patients on AS.

Nutritional Supplements

Several studies have examined the effects of nutritional supplements during AS. While none have specifically evaluated their impact on delaying the initiation of definitive treatment, they have assessed changes in PSA levels and repeat biopsy results.

An open-label trial by Marshall et al. investigated the effects of supplementation with 4,000 IU daily of vitamin D_3 for 1 year in 52 men undergoing AS.[22] A significant reduction in baseline PSA levels was observed, with 55% of the participants showing either a decrease in the number of positive cores or a reduction in the Gleason score on repeat biopsy.

Beyond vitamin D, antioxidant vitamins have been investigated. In an RCT by Hoenjet et al., an antioxidant supplement containing vitamin E (350 mg), selenium (200 µg), vitamin C (750 mg), and coenzyme Q10 (200 mg) was tested against a placebo in 80 patients with prostate cancer and rising PSA levels while on watchful waiting or following previous treatment.[23] After 21 days, no significant benefits were observed in PSA, testosterone, dihydrotestosterone, luteinizing hormone, or sex hormone-binding globulin levels, suggesting that short-term antioxidant supplementation may not meaningfully impact PSA kinetics.

Several plant-derived compounds have also been explored. Zhang et al. investigated the effects of a whole tomato supplement providing 10 mg of lycopene daily for 6 months in an open-label study of 20 men with prostate cancer on AS or who had not undergone any active treatment in the past 3 months.[24] Two participants withdrew due to rapidly increasing PSA levels and subsequently initiated active treatment. However, PSA velocity significantly decreased compared with baseline among those who completed the trial.

Another open-label trial by Sumiyoshi et al. evaluated the effects of 4.5 g per day of a patented mushroom mycelium extract in 74 prostate cancer patients undergoing watchful waiting.[25] After 6 months, only one participant experienced a decline in PSA greater than 50%. However, PSA levels remained stable among the remaining participants. Interestingly, those with high baseline anxiety reported statistically significant symptom relief, suggesting another potential benefit of naturopathic interventions during AS. Active surveillance involves living in a state of uncertainty regarding definitive treatment, which can result in feelings of anxiety for some patients. In fact, 10% of patients who decide to transition from AS to definitive treatment do so because of their anxiety, not the progression of the disease.[26]

In a double-blind, placebo-controlled RCT, 53 men with prostate cancer on AS received a supplement containing a combination of fermented soy isoflavones and mushroom polysaccharides daily or a placebo for 6 months.[27] Following the blinded trial, the men were enrolled in an open-label study with the same supplement. While more men in the treatment group experienced a decrease or stabilization of their PSA, the difference did not reach statistical significance between the two groups.

Broccoli intake has been linked to favourable gene expression changes in prostate cancer.[28] Traka et al. randomized 49 men on AS to consume standard broccoli soup or soups containing experimental broccoli genotypes with three-fold and seven-fold higher glucoraphanin concentrations. After 1 year, sequential prostate tissue biopsies revealed increased expression of genes associated with cancer progression in the control group, while the experimental arms both demonstrated more favourable gene expression profiles.

In a larger placebo-controlled RCT, Thomas et al. assessed a combination product containing extracts from pomegranate, green tea, broccoli, and turmeric in 199 men undergoing AS or watchful waiting following previous interventions.[29] After 6 months, those in the intervention group had a significantly lower percentage rise in PSA levels (14.7% vs. 78.5% in the control group), though no effect was observed on Gleason grade.

The role of dietary fats has also been investigated during AS. In a 2024 RCT by Aronson et al., 100 men on AS were randomized to either a low omega-6 fatty acid diet supplemented with fish oil capsules (2,200 mg per day) or a control group.[30] After 1 year, the intervention group experienced a 15% decrease in the Ki-67 tumour proliferation index, whereas the control group showed a 24% increase, a statistically significant difference. Ki-67 is a protein that serves as a marker for cell proliferation, and a higher Ki-67 index typically reflects more aggressive tumour behaviour.

Combined Approaches

Multimodal lifestyle approaches may have a greater impact than isolated interventions for optimizing prostate cancer management

during AS and more closely reflect the way naturopathic doctors practice. In 2005, Ornish et al. reported an RCT of 93 men with PSA levels between 4 and 10 ng/mL and Gleason scores < 7 who were undergoing AS.[31] Participants were randomized to either an intensive lifestyle and supplement intervention group or a usual care group. The intervention group followed a low-fat, plant-based diet supplemented with soy (one serving of tofu and 58 g of a fortified soy protein beverage daily), fish oil (3,000 mg/day), vitamin E (400 IU/day), selenium (200 µg/day), and vitamin C (2,000 mg/day). Additional components included moderate aerobic exercise (walking 30 minutes, 6 days per week), stress management techniques (yoga-based stretching, breathing exercises, meditation, imagery, and progressive muscle relaxation for 60 minutes daily), and participation in a weekly 1-hour support group.

After 1 year, 14% of the men in the control group initiated conventional treatment due to rising PSA and/or MRI-confirmed disease progression, whereas none of the participants in the intervention group required treatment.[31] PSA levels decreased by 4% in the intervention group while increasing by 6% in the control group ($p = 0.016$). Additionally, serum from participants in the intervention group inhibited prostate cancer cell growth in vitro by 70% compared with 9% in the control group ($p < 0.001$).

In a follow-up study, Frattaroli et al. examined clinical outcomes of these patients after 2 years.[32] By this time, 27% of control group participants, compared with only 5% of intervention participants, had initiated definitive treatment ($p < 0.05$). These findings suggest that a comprehensive lifestyle intervention combining diet, exercise, stress management, and supplementation may significantly delay disease progression in men undergoing AS.

Ornish et al. also conducted a genetic assessment of 30 patients following the same lifestyle and supplement protocol.[33] After 3 months, significant changes were noted in the expression of multiple genes regulating biological processes involved in tumorigenesis in prostate cells. Consistent with the findings from both the initial and follow-up trials, participants also experienced significant improvements in body mass index (BMI), waist circumference, lipid profiles, and blood pressure.

Another study was conducted in 2016 by Berg et al., which included 235 men with low- and low-intermediate-risk prostate cancer on AS.[34] Participants followed a diet that eliminated red meat, fried foods, dairy products, and refined carbohydrates while emphasizing fish, poultry, fresh and cruciferous vegetables, green tea, red wine, soy milk, and flax seeds. They were also placed on several supplements, including a glucosinolate/antioxidant combination product (3 capsules/day), omega-3 fatty acids (2,000 mg/day), vitamin D_3 (5,000 IU/day), a mushroom mycelium extract (3 capsules/day), a lycopene, antioxidant and phytosterol complex (2 capsules/day), a combination of fermented soy isoflavones and mushroom polysaccharides (2,000 mg/day), and a combination herbal product designed to reduce inflammation (3 capsules/day). After a median follow-up of 3.5 years, the overall survival for the participants was 99.6%, with a disease-specific survival of 100%. Only 11% of participants went on to receive active treatment.

A 2017 study by Eriksen et al. also explored the impact of combined lifestyle interventions, this time focusing on high whole-grain rye intake and vigorous physical activity.[35] Twenty-six men with non-aggressive prostate cancer undergoing AS were randomized to either the intervention group or the control group. The intervention group consumed 170 g/day of whole-grain rye and engaged in three weekly 45-minute sessions of vigorous physical activity for 6 months. While there were no significant effects on prostate cancer progression, the intervention did show improvements in aerobic fitness (VO2 peak), suggesting that even short-term changes in diet and physical activity may offer benefits for prostate health, while also promoting general wellness.

Most recently, a 2021 study by Campbell et al. investigated a multimodal approach in 68 men with very-low-risk or low-risk prostate cancer.[36] Patients followed a diet excluding animal-based products and foods high in omega-6 fatty acids while taking a supplement regimen consisting of omega-3 fatty acids (720 mg/day), curcumin (2,000 mg/day), vitamin D_3 (titrated to achieve a serum level of 150 nmol/L), and a vitamin B-complex (1,000 mg, four times weekly). Monitoring included repeat biopsies performed as clinically indicated or after 9 months. Men with higher baseline vitamin D levels were twice as likely to have a downward PSA trend ($p = 0.04$). Of the 55 patients who underwent repeat biopsy, none showed disease progression, suggesting that this combined dietary and supplement approach may help stabilize low-risk prostate cancer in the AS setting.

NATURAL INTERVENTIONS BEFORE PROSTATECTOMY

While this review focused on diet and lifestyle interventions, specifically during AS, researchers have also examined natural interventions in the pre-surgical period. This small window, typically only 2 to 4 weeks, provides a unique opportunity to assess biological effects in a controlled setting by comparing changes in tumour biomarkers, gene expression, and other molecular pathways in tissue samples from the initial biopsy and prostatectomy.

Lycopene has shown potential benefits in this period. A 2002 study found that 30 mg/day of lycopene led to smaller tumours, a higher rate of organ-confined disease, and lower PSA levels.[37] A 2017 study reported PSA reduction only in intermediate-risk patients consuming tomato products, while a more complex intervention adding selenium, omega-3s, and other polyphenols showed no benefit.[38]

Sources of phytoestrogenic compounds have been studied with varying effects. Flaxseed (*Linum usitatissimum*) supplementation (30 g/day) reduced tumour proliferation markers in one trial,[39] whereas studies on isoflavones from soy and red clover (*Trifolium pratense*) have found no significant effects on PSA or tumour characteristics.[40-42]

Green tea (*Camellia sinensis*) polyphenols have demonstrated potential. One trial found that green tea consumption significantly reduced nuclear factor kappa B activity in prostate tissue and oxidative stress markers in urine.[43] However, no significant changes in markers of proliferation, apoptosis, or oxidation were observed. Other studies have found significant reductions in serum PSA, hepatocyte growth factor, and vascular endothelial

growth factor with supplementation of a concentrated green tea polyphenol extract.[44,45]

Other natural compounds have also shown some biological activity. While pomegranate consumption increased its metabolite, urolithin-A, in prostate tissue, no changes in PSA or DNA damage markers were observed.[46] Diindolylmethane supplementation led to a decrease in PSA in 71% of participants and nuclear exclusion of androgen receptors, though the clinical significance of this latter finding remains unclear.[47] Cranberry extract also significantly reduced PSA levels in one study,[48] while high-dose silybin-phytosome from milk thistle (*Silybum marianum*) did not.[49]

Other trials have explored omega-3 supplementation. A study comparing a low-fat, fish oil-enriched (5 g/day) diet to a Western diet found reduced Ki-67 expression and altered tissue fatty acid composition.[50] However, another trial supplementing eicosapentaenoic acid (3 g/day) found no effect on Ki-67.[51]

Overall, while pre-surgical interventions with certain compounds, such as lycopene, flaxseed, green tea, diindolylmethane, cranberry, and fish oil, show promise in modulating prostate cancer biomarkers, findings remain inconsistent overall. Given the short duration of these trials, further research is needed to determine which interventions may have meaningful long-term benefits for patients with prostate cancer undergoing AS.

DISCUSSION AND CONLUSION

The increasing use of AS for low-risk prostate cancers presents a unique opportunity to explore complementary interventions that may help delay disease progression while optimizing overall health. This review examined the role of diet, exercise, and nutritional supplements during AS, revealing a complex and evolving body of evidence. While some studies suggest potential benefits, others expose inconsistent findings. Several key themes emerge when considering the implications for naturopathic practice.

Dietary interventions have been widely studied, with observational data suggesting that plant-based and Mediterranean diets may be associated with lower rates of Gleason-grade progression.[15-16] However, RCTs have yet to demonstrate a consistent benefit in preventing disease progression.[18] These mixed results may stem from the challenge of capturing the long-term effects of dietary patterns within relatively short study durations, as well as variability in dietary adherence and self-reported data. Additionally, individual dietary components may exert only modest effects when studied in isolation, whereas a broader dietary strategy may offer more meaningful clinical benefits.

Several mechanisms may help explain why plant-based and Mediterranean-style diets could influence prostate cancer progression. These dietary patterns are rich in antioxidants and phytochemicals with anti-inflammatory properties, primarily from vegetables, fruits, legumes, and whole grains.[52] Increased intake of these foods may help reduce oxidative stress and chronic inflammation, both of which are implicated in carcinogenesis and tumour progression.[53] At the same time, reducing intake of animal-based foods may limit exposure to potentially harmful compounds such as hormones and carcinogenic byproducts like heterocyclic amines produced during high-heat cooking.[54] Notably, one prospective study found that higher post-diagnostic consumption of poultry with skin and eggs was associated with a two-fold increased risk of prostate cancer recurrence or progression, with risk magnified among men with high prognostic risk at diagnosis.[55] This association may be explained by heterocyclic amine exposure from grilled or broiled poultry skin and elevated dietary choline from eggs, both of which have been implicated in prostate cancer pathogenesis.[54,55] Diets high in animal protein have also been associated with insulin resistance and elevated circulating insulin levels,[56] while milk and dairy products may increase levels of insulin-like growth factor 1, a hormone linked to prostate cancer risk.[57] Furthermore, ecological studies have shown a positive association between high national intake of animal products and increased prostate cancer incidence and mortality.[58,59] These findings support the biological plausibility of dietary modulation as a strategy to reduce progression risk during AS.

Despite the limitations in prostate cancer–specific outcomes, the well-established cardiometabolic and anti-inflammatory advantages of plant-forward diets make them a reasonable and evidence-informed recommendation for patients undergoing AS.[52,60-61] This is particularly relevant given that cardiovascular disease–related mortality is a major competing risk in men with localized prostate cancer, with large-scale data indicating that cardiovascular disease–related deaths exceed prostate cancer–related deaths almost immediately in low- and intermediate-risk patients and within 7.5 years in high-risk patients.[62] This study highlights that, for men with localized prostate cancer, cardiovascular disease quickly surpasses cancer as the leading cause of death, particularly among those with lower-risk profiles. The findings underscore the necessity of addressing cardiovascular health in conjunction with cancer progression as a key consideration in developing comprehensive, integrative treatment plans during AS.

Exercise has shown promise in the context of prostate cancer, with the only RCT to date reporting significant reductions in PSA levels following a 12-week HIIT program.[21] However, observational studies have produced inconsistent findings regarding the relationship between PA and AS outcomes.[17,19-20] While the direct effects of exercise on prostate cancer progression remain uncertain, its benefits for overall health, immune function, cardiometabolic health and inflammation regulation reinforce its importance as a cornerstone of supportive care for patients undergoing AS.[63-66]

Research on nutritional supplements has produced variable results, with some interventions, such as vitamin D_3, several plant-derived compounds, and fish oil, showing reductions in PSA levels and favourable biopsy findings (Table 1). In contrast, others, such as antioxidant combinations and soy isoflavones, have demonstrated little to no effect.[23,27] Green tea polyphenols have been investigated in the pre-surgical setting, with findings suggesting potential systemic effects, including reductions in PSA and markers of inflammation and oxidative stress.[43-45] However, the bioavailability of green tea polyphenols in prostate tissue is low, which may explain the lack of significant tissue biomarker changes in some trials. Research approaching prostatectomy has also explored other dietary and supplement interventions, with

TABLE 1 Selected Nutritional Supplements Studied in Prostate Cancer Active Surveillance

Supplement	Studied Dose	Potential Role
Vitamin D_3	2,000–5,000 IU/day, titrated to 25(OH)D of 75–150 nmol/L	Immune modulation, anti-inflammatory, antiproliferative effects
Fish-derived omega-3 fatty acids (EPA/DHA)	1,000–3,000 mg/day of combined EPA/DHA	Anti-inflammatory, may influence tumour microenvironment
Green tea polyphenols (EGCG)	200–400 mg twice daily	Antioxidant, inhibits cell proliferation, induces apoptosis
Lycopene	15–30 mg/day from supplements or tomato products	Antioxidant, may inhibit IGF-1 signalling and reduce oxidative stress
Mushroom mycelial extract	1.5–4.5 g/day	Immunomodulatory; potential to enhance natural killer cell activity and immune surveillance
Ground flaxseed	30 g/day	Rich in lignans and omega-3s, may reduce tumour proliferation markers
Diindolylmethane	225 mg twice daily	May lower PSA and affect androgen receptor signalling
Cranberry extract	1,500 mg/day cranberry fruit powder	May reduce PSA; antioxidant and anti-adhesion effects

DHA = docosahexanoic acid; EGCG = epigallocatechin-3-gallate; EPA = eicosapentanoic acid; IGF = insulin-like growth factors; PSA = prostate-specific antigen.

CLINICAL PEARLS FOR NATUROPATHIC SUPPORT DURING ACTIVE SURVEILLANCE (AS) IN PROSTATE CANCER

- **Dietary patterns matter** – Plant-based, low-fat, and Mediterranean diets are associated with lower rates of Gleason-grade progression and improved cardiometabolic health. Patients should be encouraged to:
  - Consume six to eight servings of vegetables (especially cruciferous vegetables and cooked tomato products) and two to three servings of fruits daily.
  - Eat whole grains or other sources of complex carbohydrates with each meal.
  - Use extra virgin olive oil as a primary fat source and aim for one to two servings of whole-food plant-based fats like nuts, seeds, and olives daily.
  - If choosing to consume animal protein, eat fish or seafood two or three times per week, white meat (chicken, turkey) without skin, no more than twice weekly, and limit eggs to four per week.
  - Limit red meat (less than two servings per week), processed meat (less than one serving per week), and sweets (less than two servings per week).
- **Exercise has systemic benefits** – Recommend at least 150 minutes/week of moderate-intensity aerobic exercise or 75 minutes of vigorous activity, with resistance training 2–3 times/week. High-intensity interval training (HIIT) protocols of 3 sessions/week for 12 weeks have shown reductions in prostate-specific antigen (PSA) levels.
- **Multimodal interventions may be most effective** – Comprehensive lifestyle strategies that include diet, exercise, stress management, and targeted supplementation have shown the greatest impact in clinical trials.
- **Cardiovascular risk surpasses prostate cancer risk** – Cardiovascular disease-related mortality exceeds prostate cancer mortality in men with localized disease, reinforcing the need for heart-healthy interventions.
- **Personalized integrative care is key** – Naturopathic doctors can optimize AS outcomes by tailoring recommendations to individual patient needs, balancing the best available evidence with holistic care principles.

several natural compounds demonstrating reductions in PSA or tumour proliferation markers such as Ki-67.[37,39,43-45,47,48,50] While these findings suggest potential biological effects, further research is needed to determine whether these interventions translate into meaningful clinical outcomes for patients undergoing AS.

Although most research on integrative interventions during AS has focused on prostate cancer, emerging studies suggest potential applications in other cancers characterized by a prolonged monitoring period before invasive treatment initiation.[67-73] Early-stage chronic lymphocytic leukemia (CLL) and monoclonal gammopathy of undetermined significance (MGUS)/smouldering multiple myeloma (SMM), all of which involve watchful waiting strategies, have also been the focus of early-stage research on natural interventions. In CLL, green tea polyphenols have shown promise in reducing disease severity, with the majority of patients experiencing a decline in lymphocyte counts and/or lymphadenopathy.[67] Similarly, vitamin D supplementation has been studied in early-stage CLL patients, demonstrating that supplementing with vitamin D was significantly associated with a longer time to first treatment in the young cohort (age ≤ 65) and a longer treatment-free survival for all ages.[68] Additional studies have explored curcumin,[69] omega-3 fatty acids,[70] extra virgin olive oil,[71] and quercetin,[72] with some evidence suggesting modulation of inflammatory and apoptotic markers. MGUS/SMM have also been investigated in the context of curcumin supplementation, with findings indicating reductions in free light chain ratios

and markers of bone resorption, suggesting a potential to slow disease progression.[73] Recently, an abstract of a single-arm pilot trial was presented at the 2024 American Society of Hematology Annual Meeting and Exposition, examining the effect of a high-fibre, plant-based diet for 12 weeks in 20 individuals with MGUS or SMM (U. Shah et al., unpublished abstract, 2024). The authors noted that participants experienced improvements in quality of life and several biomarkers related to metabolic health, gut microbiome diversity, and inflammation. Although the trial's small size limits broader conclusions, remarkably, two patients with progressive disease experienced disease stabilization while following the diet. While these findings are preliminary, they highlight the growing interest in the use of natural interventions to better manage slowly progressive early-stage cancers or precancerous conditions alongside active monitoring. This further reinforces the need for additional research on multimodal approaches that may provide additional benefits beyond conventional surveillance in multiple settings.

A critical limitation of the current body of research is the tendency to study interventions in isolation, which does not align with the holistic and integrative approach used in naturopathic practice. Many complementary interventions may have synergistic effects when combined, as suggested by multimodal trials such as the Ornish et al. study.[33] In this trial, a combination of a plant-based diet, exercise, stress management, and supplementation resulted in significantly lower PSA levels and delayed treatment initiation compared with usual care. Similarly, Berg et al. and Campbell et al. demonstrated that a structured dietary and supplement regimen was associated with favourable PSA trends and a lack of disease progression on repeat biopsy.[34,36] Taken together, these findings suggest that a comprehensive lifestyle approach may be more impactful than any single intervention alone. Future research should focus on evaluating multimodal interventions with longer follow-up periods, standardized protocols, and clinically relevant endpoints to better reflect real-world applications of integrative oncology care.

For naturopathic doctors, these insights reinforce the importance of personalized, evidence-informed strategies that integrate multiple modalities to optimize patient outcomes. Although we do not have enough evidence to definitively recommend integrative interventions across the board in AS, until more conclusive evidence emerges, naturopathic doctors can play a key role in guiding motivated patients through AS with tailored recommendations that align with both the available research and the principles of holistic, patient-centred care.

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CONFLICTS OF INTEREST DISCLOSURE

We have read and understood the *CAND Journal*'s policy on conflicts of interest and declare that we have none.

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