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.

REFERENCES

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2017. Canadian Cancer Society; 2017.
2. Etzioni R, Gulati R, Falcon S, et al. Quantifying the role of PSA screening in the US prostate cancer mortality decline. *Cancer Causes Control.* 2008;19(2):175-181. https://doi.org/10.1007/s10552-007-9083-8
3. Goldberg H, Klaassen Z, Chandrasekar T, Fleshner N. Preventing clinical progression and need for treatment in patients on active surveillance for prostate cancer. *Curr Opin Urol.* 2018;28(1):46-54. https://doi.org/10.1097/MOU.0000000000000455
4. Hoffman KE, Penson DF, Zhao Z, et al. Patient-reported outcomes through 5 years for active surveillance, surgery, brachytherapy, or external beam radiation with or without androgen deprivation therapy for localized prostate cancer. *JAMA.* 2020;323(2):149-163. https://doi.org/10.1001/jama.2019.20675
5. Morash C, Tey R, Agbassi C, et al. Active surveillance for the management of localized prostate cancer: Guideline recommendations. *Can Urol Assoc J.* 2015;9(5-6):171-178. https://doi.org/10.5489/cuaj.2806
6. Robinson D, Abdulkareem R, Nasrollah D, et al. Frequency of biopsy and tumor grade before vs after introduction of prostate magnetic resonance imaging. *JAMA Netw Open.* 2023;6(8):e2330233. https://doi.org/10.1001/jamanetworkopen.2023.30233
7. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol.* 2015;33(3):272-277. https://doi.org/10.1200/JCO.2014.55.1192
8. Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. *J Clin Oncol.* 2015;33(30):3379-3385. https://doi.org/10.1200/JCO.2015.62.5764
9. Hill J, Hodsdon W, Schor J, et al. Naturopathic oncology modified Delphi panel. *Integr Cancer Ther.* 2016;15(1):69-79. https://doi.org/10.1177/1534735415589983
10. Marsden E, Nigh G, Birdsall S, Wright H, Traub M. Oncology Association of Naturopathic Physicians: Principles of care guidelines. *Curr Oncol.* 2019;26(1):12-18. https://doi.org/10.3747/co.26.4815
11. Zuniga KB, Zhao S, Kenfield SA, et al. Trends in complementary and alternative medicine use among patients with prostate cancer. *J Urol.* 2019;202(4):689-695. https://doi.org/10.1097/JU.0000000000000336
12. Gregg JR, Zheng J, Lopez DS, et al. Diet quality and Gleason grade progression among localised prostate cancer patients on active surveillance. *Br J Cancer.* 2019;120(4):466-471. https://doi.org/10.1038/s41416-019-0380-2
13. Su ZT, Mamawala M, Landis PK, et al. Diet quality, dietary inflammatory potential, and risk of prostate cancer grade reclassification. *JAMA Oncol.* 2024;10(12):1702-1706. https://doi.org/10.1001/jamaoncol.2024.4406
14. Schenk JM, Liu M, Neuhouser ML, et al. Dietary patterns and risk of Gleason grade progression among men on active surveillance for prostate cancer: results from the canary prostate active surveillance study. *Nutr Cancer.* 2023;75(2):618-626. https://doi.org/10.1080/01635581.2022.2143537
15. Gregg JR, Zhang X, Chapin BF, et al. Adherence to the Mediterranean diet and grade group progression in localized prostate cancer: an active surveillance cohort. *Cancer.* 2021;127(5):720-728. https://doi.org/10.1002/cncr.33182
16. Liu VN, Van Blarigan EL, Zhang L, et al. Plant-based diets and disease progression in men with prostate cancer. *JAMA Netw Open.* 2024;7(5):e249053. https://doi.org/10.1001/jamanetworkopen.2024.9053
17. Vandersluis AD, Guy DE, Klotz LH, et al. The role of lifestyle characteristics on prostate cancer progression in two active surveillance cohorts. *Prostate Cancer Prostatic Dis.* 2016;19(3):305-310. https://doi.org/10.1038/pcan.2016.22
18. Parsons JK, Zahrieh D, Mohler JL, et al. Effect of a behavioral intervention to increase vegetable consumption on cancer progression among men with early-stage prostate cancer: the MEAL randomized clinical trial. *JAMA.* 2020;323(2):140-148. https://doi.org/10.1001/jama.2019.20207
19. Papadopoulos E, Alibhai SMH, Tomlinson GA, et al. Influence of physical activity on active surveillance discontinuation in men with low-risk prostate cancer. *Cancer Causes Control.* 2019;30(9):1009-1012. https://doi.org/10.1007/s10552-019-01211-0
20. Brassetti A, Ferriero M, Napodano G, et al. Physical activity decreases the risk of cancer reclassification in patients on active surveillance: a multicenter retrospective study. *Prostate Cancer Prostatic Dis.* 2021;24(4):1151-1157. https://doi.org/10.1038/s41391-021-00375-8

21. Kang DW, Fairey AS, Boulé NG, Field CJ, Wharton SA, Courneya KS. Effects of exercise on cardiorespiratory fitness and biochemical progression in men with localized prostate cancer under active surveillance: the ERASE randomized clinical trial. *JAMA Oncol.* 2021;7(10):1487-1495. https://doi.org/10.1001/jamaoncol.2021.3067

22. Marshall DT, Savage SJ, Garrett-Mayer E, et al. Vitamin D3 supplementation at 4000 international units per day for one year results in a decrease of positive cores at repeat biopsy in subjects with low-risk prostate cancer under active surveillance. *J Clin Endocrinol Metab*. 2012;97(7):2315-2324. https://doi.org/10.1210/jc.2012-1451

23. Hoenjet KM, Dagnelie PC, Delaere KP, Wijckmans NE, Zambon JV, Oosterhof GO. Effect of a nutritional supplement containing vitamin E, selenium, vitamin C and coenzyme Q10 on serum PSA in patients with hormonally untreated carcinoma of the prostate: a randomised placebo-controlled study. *Eur Urol.* 2005;47(4):433-440. https://doi.org/10.1016/j.eururo.2004.11.017

24. Zhang X, Yang Y, Wang Q. Lycopene can reduce prostate-specific antigen velocity in a phase II clinical study in Chinese population. *Chin Med J (Engl).* 2014;127(11):2143-2146.

25. Sumiyoshi Y, Hashine K, Kakehi Y, et al. Dietary administration of mushroom mycelium extracts in patients with early-stage prostate cancers managed expectantly: a phase II study. *Jpn J Clin Oncol.* 2010;40(10):967-972. https://doi.org/10.1093/jjco/hyq081

26. Bokhorst LP, Valdagni R, Rannikko A, et al; PRIAS study group. A decade of active surveillance in the PRIAS study: an update and evaluation of the criteria used to recommend a switch to active treatment. *Eur Urol.* 2016;70(6):954-960. https://doi.org/10.1016/j. eururo.2016.06.007

27. deVere White RW, Tsodikov A, Stapp EC, et al. Effects of a high dose, aglycone-rich soy extract on prostate-specific antigen and serum isoflavone concentrations in men with localized prostate cancer. *Nutr Cancer.* 2010;62(8):1036-1043. https://doi.org/10.1080/01635581.2010.492085

28. Traka MH, Melchini A, Coode-Bate J, et al. Transcriptional changes in prostate of men on active surveillance after a 12-mo glucoraphanin-rich broccoli intervention—results from the Effect of Sulforaphane on prostate CAncer PrEvention (ESCAPE) randomized controlled trial. *Am J Clin Nutr.* 2019;109(4):1133-1144. https://doi.org/10.1093/ajcn/nqz012

29. Thomas R, Williams M, Sharma H, Chaudry A, Bellamy P. A double-blind, placebo-controlled randomised trial evaluating the effect of a polyphenol-rich whole food supplement on PSA progression in men with prostate cancer—the U.K. NCRN Pomi-T study. *Prostate Cancer Prostatic Dis.* 2014;17(2):180-186. https://doi.org/10.1038/pcan.2014.6

30. Aronson WJ, Grogan T, Liang P, et al. High omega-3, low omega-6 diet with fish oil for men with prostate cancer on active surveillance: the CAPFISH-3 randomized clinical trial. *J Clin Oncol*. https://doi.org/10.1200/JCO.24.00608

31. Ornish D, Weidner G, Fair WR, et al. Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol.* 2005;174(3):1065-1070. https://doi.org/10.1097/01.ju.0000169487.49018.73

32. Frattaroli J, Weidner G, Dnistrian AM, et al. Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. *Urology.* 2008;72(6):1319-1323. https://doi.org/10.1016/j.urology.2008.04.050

33. Ornish D, Magbanua MJ, Weidner G, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. *Proc Natl Acad Sci USA*. 2008;105(24):8369-8374. https://doi.org/10.1073/pnas.0803080105

34. Berg CJ, Habibian DJ, Katz AE, Kosinski KE, Corcoran AT, Fontes AS. Active holistic surveillance: the nutritional aspect of delayed intervention in prostate cancer. *J Nutr Metab.* 2016;2016:2917065. https://doi.org/10.1155/2016/2917065

35. Eriksen AK, Hansen RD, Borre M, et al. A lifestyle intervention among elderly men on active surveillance for non-aggressive prostate cancer: a randomised feasibility study with whole-grain rye and exercise. *Trials.* 2017;18(1):20. https://doi.org/10.1186/s13063-016-1734-1

36. Campbell RA, Li J, Malone L, Levy DA. Correlative analysis of vitamin D and omega-3 fatty acid intake in men on active surveillance for prostate cancer. *Urology.* 2021;155:110-116. https://doi.org/10.1016/j.urology.2021.04.050

37. Kucuk O, Sarkar FH, Djuric Z, et al. Effects of lycopene supplementation in patients with localized prostate cancer. *Exp Biol Med (Maywood).* 2002;227(10):881-885. https://doi.org/10.1177/153537020222701007

38. Paur I, Lilleby W, Bøhn SK, et al. Tomato-based randomized controlled trial in prostate cancer patients: effect on PSA. *Clin Nutr.* 2017;36(3):672-679. https://doi.org/10.1016/j.clnu.2016.06.014

39. Demark-Wahnefried W, Polascik TJ, George SL, et al. Flaxseed supplementation (not dietary fat restriction) reduces prostate cancer proliferation rates in men presurgery. *Cancer Epidemiol Biomarkers Prev.* 2008;17(12):3577-3587. https://doi.org/10.1158/1055-9965.EPI-08-0008

40. Hamilton-Reeves JM, Banerjee S, Banerjee SK, et al. Short-term soy isoflavone intervention in patients with localized prostate cancer: a randomized, double-blind, placebo-controlled trial. *PLoS One.* 2013;8(7):e68331. https://doi.org/10.1371/journal.pone.0068331

41. Lokeshwar SD, Ali A, Weiss TR, et al. The effect of a fermented soy beverage among patients with localized prostate cancer prior to radical prostatectomy. *BMC Urol.* 2024;24(1):102. https://doi.org/10.1186/s12894-024-01483-y

42. Jarred RA, Keikha M, Dowling C, et al. Induction of apoptosis in low to moderate-grade human prostate carcinoma by red clover-derived dietary isoflavones. *Cancer Epidemiol Biomarkers Prev.* 2002;11(12):1689-1696.

43. Henning SM, Wang P, Said JW, et al. Randomized clinical trial of brewed green and black tea in men with prostate cancer prior to prostatectomy. *Prostate.* 2015;75(5):550-559. https://doi.org/10.1002/pros.22943

44. McLarty J, Bigelow RL, Smith M, et al. Tea polyphenols decrease serum levels of prostate-specific antigen, hepatocyte growth factor, and vascular endothelial growth factor in prostate cancer patients and inhibit production of hepatocyte growth factor and vascular endothelial growth factor in vitro. *Cancer Prev Res (Phila).* 2009;2(7):673-682. https://doi.org/10.1158/1940-6207.CAPR-08-0167

45. Nguyen MM, Ahmann FR, Nagle RB, et al. Randomized, double-blind, placebo-controlled trial of polyphenon E in prostate cancer patients before prostatectomy: evaluation of potential chemopreventive activities. *Cancer Prev Res (Phila).* 2012;5(2):290-298. https://doi.org/10.1158/1940-6207.CAPR-11-0306

46. Freedland SJ, Carducci M, Kroeger N, et al. A double-blind, randomized, neoadjuvant study of the tissue effects of POMx pills in men with prostate cancer before radical prostatectomy. *Cancer Prev Res (Phila).* 2013;6(10):1120-1127. https://doi.org/10.1158/1940-6207.CAPR-12-0423

47. Hwang C, Sethi S, Heilbrun LK, et al. Anti-androgenic activity of absorption-enhanced 3, 3'-diindolylmethane in prostatectomy patients. *Am J Transl Res.* 2016;8(1):166-176.

48. Student V, Vidlar A, Bouchal J, et al. Cranberry intervention in patients with prostate cancer prior to radical prostatectomy. Clinical, pathological and laboratory findings. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2016;160(4):559-565. https://doi.org/10.5507/bp.2016.056

49. Flaig TW, Glodé M, Gustafson D, et al. A study of high-dose oral silybin-phytosome followed by prostatectomy in patients with localized prostate cancer. *Prostate.* 2010;70(8):848-855. https://doi.org/10.1002/pros.21118

50. Aronson WJ, Kobayashi N, Barnard RJ, et al. Phase II prospective randomized trial of a low-fat diet with fish oil supplementation in men undergoing radical prostatectomy. *Cancer Prev Res (Phila).* 2011;4(12):2062-2071. https://doi.org/10.1158/1940-6207.CAPR-11-0298

51. Robitaille K, Guertin MH, Jamshidi A, et al. A phase IIb randomized placebo-controlled trial testing the effect of MAG-EPA long-chain omega-3 fatty acid dietary supplement on prostate cancer proliferation. *Commun Med (Lond).* 2024;4(1):56. https://doi.org/10.1038/s43856-024-00456-4

52. Itsiopoulos C, Mayr HL, Thomas CJ. The anti-inflammatory effects of a Mediterranean diet: a review. *Curr Opin Clin Nutr Metab Care.* 2022;25(6):415-422. https://doi.org/10.1097/MCO.0000000000000872

53. Antonucci L, Karin M. The past and future of inflammation as a target to cancer prevention. *Cancer Prev Res (Phila).* 2024;17(4):141-155. https://doi.org/10.1158/1940-6207.CAPR-23-0423

54. Rohrmann S, Nimptsch K, Sinha R, et al. Intake of meat mutagens and risk of prostate cancer in a cohort of U.S. health professionals. *Cancer Epidemiol Biomarkers Prev.* 2015;24(10):1557-1563. https://doi.org/10.1158/1055-9965.EPI-15-0068-T

55. Richman EL, Stampfer MJ, Paciorek A, Broering JM, Carroll PR, Chan JM. Intakes of meat, fish, poultry, and eggs and risk of prostate cancer progression. *Am J Clin Nutr*. 2010;91(3):712-721. https://doi.org/10.3945/ajcn.2009.28474

56. Azemati B, Rajaram S, Jaceldo-Siegl K, et al. Animal-protein intake is associated with insulin resistance in Adventist Health Study 2 (AHS-2) calibration substudy participants: a cross-sectional analysis. *Curr Dev Nutr.* 2017;1(4):e000299. https://doi.org/10.3945/cdn.116.000299

57. Harrison S, Lennon R, Holly J, et al. Does milk intake promote prostate cancer initiation or progression via effects on insulin-like growth factors (IGFs)? A systematic review and meta-analysis. *Cancer Causes Control.* 2017;28(6):497-528. https://doi.org/10.1007/s10552-017-0883-1

58. Penuelas J, Krisztin T, Obersteiner M, et al. Country-level relationships of the human intake of N and P, animal and vegetable food, and alcoholic beverages with cancer and life expectancy. *Int J Environ Res Public Health.* 2020;17(19):7240. https://doi.org/10.3390/ijerph17197240

59. Grant WB. A multicountry ecologic study of risk and risk reduction factors for prostate cancer mortality. *Eur Urol.* 2004;45(3):271-279. https://doi.org/10.1016/j.eururo.2003.08.018

60. Laffond A, Rivera-Picón C, Rodríguez-Muñoz PM, et al. Mediterranean diet for primary and secondary prevention of cardiovascular disease and mortality: an updated systematic review. *Nutrients.* 2023;15(15):3356. https://doi.org/10.3390/nu15153356

61. Capodici A, Mocciaro G, Gori D, et al. Cardiovascular health and cancer risk associated with plant-based diets: an umbrella review. *PLoS One.* 2024;19(5):e0300711. https://doi.org/10.1371/journal.pone.0300711

62. Luo Z, Chi K, Zhao H, et al. Cardiovascular mortality by cancer risk stratification in patients with localized prostate cancer: a SEER-based study. *Front Cardiovasc Med.* 2023;10:1130691. https://doi.org/10.3389/fcvm.2023.1130691

63. Reiner M, Niermann C, Jekauc D, Woll A. Long-term health benefits of physical activity—a systematic review of longitudinal studies. *BMC Public Health.* 2013;13:813. https://doi.org/10.1186/1471-2458-13-813

64. Simpson RJ, Kunz H, Agha N, Graff R. Exercise and the regulation of immune functions. *Prog Mol Biol Transl Sci.* 2015;135:355-380. https://doi.org/10.1016/bs.pmbts.2015.08.001

65. Isath A, Koziol KJ, Martinez MW, et al. Exercise and cardiovascular health: a state-of-the-art review. *Prog Cardiovasc Dis.* 2023;79:44-52. https://doi.org/10.1016/j.pcad.2023.04.008

66. Alizaei Yousefabadi H, Niyazi A, Alaee S, Fathi M, Mohammad Rahimi GR. Anti-inflammatory effects of exercise on metabolic syndrome patients: a systematic review and meta-analysis. *Biol Res Nurs.* 2021;23(2):280-292. https://doi.org/10.1177/1099800420958068

67. Shanafelt TD, Call TG, Zent CS, et al. Phase 2 trial of daily, oral Polyphenon E in patients with asymptomatic, Rai stage 0 to II chronic lymphocytic leukemia. *Cancer.* 2013;119(2):363-370. https://doi.org/10.1002/cncr.27719

68. Tadmor T, Melamed G, Alapi H, et al. Vitamin D supplement for patients with early-stage chronic lymphocytic leukemia is associated with a longer time to first treatment. *Blood Adv.* 2024;8(14):3840-3846. https://doi.org/10.1182/bloodadvances.2023011458

69. William BM, Brillhart K, Afable M, et al. A phase II study of curcumin and vitamin D in previously untreated patients with early-stage chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). *Blood.* 2018;132(Suppl 1):1875. https://doi.org/10.1182/blood-2018-99-112295

70. Fahrmann JF, Ballester OF, Ballester G, et al. Inhibition of nuclear factor kappa B activation in early-stage chronic lymphocytic leukemia by omega-3 fatty acids. *Cancer Invest.* 2013;31(1):24-38. https://doi.org/10.3109/07357907.2012.743553

71. Rojas Gil AP, Kodonis I, Ioannidis A, et al. The effect of dietary intervention with high-oleocanthal and oleacein olive oil in patients with early-stage chronic lymphocytic leukemia: a pilot randomized trial. *Front Oncol.* 2022;11:810249. https://doi.org/10.3389/fonc.2021.810249

72. Baron BW, Thirman MJ, Giurcanu MC, Baron JM. Quercetin therapy for selected patients with PIM1 kinase-positive chronic lymphocytic leukemia/small lymphocytic lymphoma: a pilot study. *Acta Haematol.* 2018;139(2):132-139. https://doi.org/10.1159/000486361

73. Golombick T, Diamond TH, Manoharan A, Ramakrishna R. Monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, and curcumin: a randomized, double-blind placebo-controlled cross-over 4g study and an open-label 8g extension study. *Am J Hematol.* 2012;87(5):455-460. https://doi.org/10.1002/ajh.23159