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Lesson 2 Volume 39

Integrative Medicine and Urology: Bladder and Prostate Cancer, Supplements and Lifestyle Changes*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to provide evidence-based lifestyle, supplement and other integrative medicine recommendations, and discourage the use of perceived integrative medicine interventions with minimal or negative clinical research.

Mark A. Moyad, MD, MPH

Disclosures: Abbvie: Lecturer (speaker for disease awareness only)

Jenkins/Pokempner Director of Preventive & Alternative Medicine
Department of Urology
University of Michigan
Ann Arbor, Michigan

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INTRODUCTION

As part of the National Institutes of Health, NCCIH (National Center for Complementary and Integrative Health) should become an ongoing resource for clinicians and patients for a variety of integrative medicine topics, products and research.[1] Examples of major subsets of IM as defined by the NCCIH are listed in Appendix 1 (online issue only). Ideally IM represents the collective goal of more objective patient education and empowerment via lifestyle changes such as dietary modifications, mind-body exercise options, dietary supplements (nutraceuticals) and other interventions. IM education is valuable because it creates awareness of not only what has the potential to be clinically effective, but also what may be ineffective or unsafe.

Few topics in medicine garner as much support and controversy among health care professionals as dietary supplements, the most commonly used form of IM.[1] Supplements can be intimidating for health care professionals to address due to a general lack of IM knowledge, discouraging initiation of open, objective discussions.[2, 3] This Update will place heavy initial emphasis on dietary supplements, followed by other IM recommendations such as greater adherence to exercise, adopting meditation and improving diet quality.

QUALITY CONTROL ISSUES, SOLUTIONS AND CANNABIDIOL

No discussion of potential efficacy should begin without addressing the most important issue concerning supplements, which is quality control or safety of the supply chain.[4-6] QC issues abound due to a lack of strict regional or even global regulation compared to conventional prescriptions. Dietary supplements are now potentially responsible for 20% of drug induced liver injury or hepatoxicity cases in the U.S. alone,[6] which is arguably the highest rate on record. The lack of rigorous, reliable QC compromises trust in IM and patient care.

Globally several reputable third party QC organizations exist which provide independent, bias-free validation and certification of products.[7] These organizations can assist in verifying the accuracy of what is claimed on the product label. Several of these companies are already well known for global QC certification, setting safety standards for electrical/electronic products and industrial equipment. Appendix 2 (online issue only) contains a list of QC companies and their contact information. Clinicians should also acquaint themselves with the pros and cons of their local private and government supplement regulatory groups since QC options vary regionally.[8]

Third party QC testing does not provide a 100% safety guarantee for patients, but it increases the probability of enhanced safety, efficacy and accountability.[7] Some form of third party verification should be the minimum threshold required before recommending use of a product. In addition to efficacy and safety data from clinical studies, cost sensitivity should be included in patient discussions about IM.

Finally, it is an educational, coincidental and hopefully relatable teaching moment for clinicians and their patients inquiring about the benefits and limitations of research on marijuana ("natural" herbal product) derivatives such as CBD (cannabidiol) in several areas of medicine. **Yet similar to dietary supplements, the lack of third party QC verification of the numerous products being offered on the Internet should be a primary part of any discussion before the debate over efficacy is initiated.[9]** When third party verification is unavailable, these companies should at least volunteer a certificate of analysis, providing proof that what is advertised on the label is precisely what is in the product itself—no more and no less.

BLADDER CANCER: LESS IS MORE EXCEPT WITH LIFESTYLE CHANGES

Patients with cancer are more likely to use IM products, especially dietary supplements, and the more invasive the conventional intervention, such as surgery for bladder cancer, the greater the prevalence of IM use postoperatively.[10] Regardless of position on the disease spectrum, out-of-pocket IM costs for cancer exceed those of any other (cancer-free) disease. Dietary supplements lead the IM cost list and should be discussed with patients. Still, conventional treatment costs associated with bladder cancer exceed those of all other cancers, and high recurrence rates contribute to those costs. This situation creates one of the best opportunities in medicine for current and future urological researchers to identify an effective, low cost, preventive supplement, diet or other IM intervention for bladder cancer.

A number of phase III dietary supplement clinical trials have been conducted with the goal of preventing recurrence of non-muscle invasive bladder cancer. **Data from these trials should be discussed with patients as a means of providing objective reasons for currently avoiding most dietary supplements rather than simply discouraging their use without referring to the evidence-based literature**. **Supplements advertised for the prevention of or as adjuvant therapy for bladder cancer will lead to an organic transition in the discussion to emphasize lifestyle changes, which allows patients the perception and reality of empowerment (personal locus of control) during the disease process, mirroring a primary reason proffered for seeking IM pill solutions.** Improved communication in this scenario cannot be overemphasized since it is a principal component of protecting patients in terms of cost and efficacy expectations.[11]

Vitamin B6 (pyridoxine). A phase III, double-blind, randomized trial was conducted to measure the effects of pyridoxine (vitamin B6) on recurrence of Ta and T1 transitional cell bladder tumors.[12] A total of 291 patients were randomized to receive 20 mg pyridoxine daily or placebo beginning 7 to 14 days after complete transurethral resection. Pyridoxine was believed to favorably impact tryptophan metabolism abnormalities, which have been observed in patients with bladder cancer. Preliminary evidence and previous studies suggested a potential benefit, and research into immune surveillance enhancement is currently under way. However, in the phase III trial no difference was demonstrated between placebo and

ABBREVIATIONS: IM (integrative medicine), LcS (Lactobacillus casei strain Shirota), QC (quality control), RDA (recommended daily allowance)

pyridoxine even after the authors adjusted for urinary tryptophan metabolite concentrations.

The other issue with vitamin B6, especially at higher doses for long periods, is the potential for toxic sensory neuropathy, which when combined with the lack of efficacy data, should discourage its use in patients with bladder cancer. Pyridoxine does have a potential clinical role in other areas of medicine such as primary hyperoxaluria type I with some preliminary data indicating reduction of hyperoxaluria in patients with recurrent calcium oxalate stones.[13] However, patients should be informed of the lack of data for bladder cancer and the potential serious neurological toxicity.

Interestingly, since clinical studies of B6 supplement for bladder cancer were initiated, lifestyle changes/dietary management and prevention of kidney stones/recurrence have become part of conventional medicine. Patients with bladder cancer may find themselves in a similar situation in the future since there is still considerable interest in the potential for cancer prevention with dietary vitamin B6 and other vitamins. Some of the highest concentrations of vitamin B6 are found in beans and lentils, fish (sockeye salmon, herring, trout), nuts and seeds, vegetables and fruits, and whole grains, all of which are heart healthy. The National Institutes of Health Office of Dietary Supplements has a website that allows health care professionals and patients to quickly access information on healthy dietary sources of nutrients, supplements and other critical information on nutraceuticals.[14]

Vitamin A, beta-carotene and cause or consequence blood tests. No difference was found for a vitamin A pharmacological oral derivative known as "fenretinide" in a phase III trial of patients with bladder cancer.[15] Interestingly another trial suggested smoking status (current/former) to be potentially associated with worse overall and cancer mortality in the intervention arm.[16] These findings are of interest because 2 notable phase III trials, ATBC (Alpha-Tocopherol, Beta-Carotene)[17] and CARET (Beta-Carotene and Retinol Efficacy Trial),[18] indicated that beta-carotene (a precursor to vitamin A) at 20 mg daily and 30 mg daily, respectively, resulted in an increase in lung cancer and all-cause mortality in current smokers. These trials have led to the general recommendation of discouraging use of individual beta-carotene supplements in smokers.[19]

In AREDS2 (Age-Related Eye Disease Study 2), a more recent phase III trial of a combination supplement for macular degeneration, 15 mg of beta-carotene resulted in an increase in lung cancer risk primarily in former smokers vs non-smokers.[20] Clinicians should recommend avoidance of beta-carotene supplementation in former and current smokers regardless of bladder cancer status, and instead suggest a multivitamin that does not contain beta-carotene.

These phase III trials create ideal opportunities for clinicians to discuss pivotal lifestyle changes such as smoking cessation and avoidance of secondhand smoke. Unprecedented excitement and optimism for beta-carotene supplements in the area of cancer prevention led to the design of these trials after numerous studies suggested that higher beta-carotene levels were associated with lower risks of cancer and cancer recurrence. However, in retrospect, higher beta-carotene levels may have been a marker of adherence to greater healthy lifestyle behaviors or a better prognostic profile.

This topic raises an opportunity to better educate patients on the concept of "cause vs consequence," and its inherent unfortunate ability to increase supplement and diagnostic company marketing opportunities and profit but not patient care. Such a discussion would allow clinicians to protect patients from a commonly misconstrued situation. Blood testing for multiple nutrients and their true correlation with so-called "hard" clinical end points is still at an embryonic stage. Value needs to be questioned in each and every instance to protect patients. A belief exists that a deficient or insufficient blood nutrient level is often the eventual cause of a medical situation and not the consequence of the condition. In addition, there is a belief that higher levels of nutrients in blood samples are the primary cause of risk reduction, and not the consequence of a more diverse healthy lifestyle pattern or a marker of health status and prognosis. Clinically construing plasma levels of micronutrients could be unreliable without knowing the impact of inflammation on these concentrations due to acute and chronic conditions.[21] This issue has been known for some time but has received minimal educational attention in urology. Appendix 3 (online issue only) contains a partial list of nutrient levels potentially impacted by inflammation or disease status.

Some nutrients function as negative acute phase reactants similar to what is observed with albumin in patients with localized vs advanced cancer. The enthusiasm of studying or correlating any nutrient with a medical condition must be tempered by the cause vs consequence objective discussion, and should be considered when the hype about any nutrient exceeds the research. The passage of time and more clinical investigation are needed to determine the objective relevance of each nutrient as well as the blood test proffered for it. Urology, like any other specialty, has been offered a variety of such tests for patients commercially without definitive validity (lycopene, selenium, vitamin E). Is this also the current case for routine vitamin D testing? This possibility exists since the accuracy of the test could be impacted by a variety of chronic inflammatory conditons.[21,22]

When a supplement such as beta-carotene or a serological test is discouraged or cannot be advocated, what is more critical than reviewing the more crucial lifestyle issues such as smoking cessation? Expecting a supplement to overcome the potential devastating effects of tobacco exposure has not proved effective and remarkably has the potential to further amplify the negative effects on all-cause morbidity and mortality.

Megadose supplements and folic acid. A small randomized trial conducted in the 1990s indicated a benefit for a megadose combination supplement compared to a RDA multivitamin product for non-muscle invasive bladder cancer following treatment with bacillus Calmette-Guérin.[23] A larger (670 patients) follow-up phase III randomized study indicated no impact of this megadose product.[24] Interestingly 2 ingredients were increased in dosage from the original megadose supplement used in the preliminary positive study compared to the phase III trial. This practice would be uncommon with a drug attempting to gain FDA (U.S. Food and Drug Administration) approval, where a preliminary effective dosage in phase I and phase II studies would remain unaltered in the definitive phase III trial. Dietary supplement trials should be expected to follow the same consistent dose directives.

In the aforementioned studies vitamin D dose was increased from 400 to 1600 IU daily and folic acid dose was increased from 0.4 to 1.6 mg daily (4 times higher than the RDA). This is of interest because folate (vitamin B9) is involved in de novo

nucleotide synthesis for potential support of rapidly proliferating tissues, and it is now known that upregulation of folate receptors can occur in multiple cancers, including bladder and prostate tumors.[25, 26] Recent prospective data have indicated the potential for synthetic folic acid supplementation to increase the risk of bladder cancer recurrence, while folate from food sources appears to reduce recurrence.[27] Folate may also have a role in the primary prevention of bladder cancer based on large meta-analyses of this particular issue.[28] Clinicians should consider discouraging individual folic acid supplements and potentially multivitamins with folic acid that contain more than the RDA (400 mg) in patients diagnosed with and treated for bladder cancer, especially in countries with mandatory dietary fortification. It also may be plausible to discourage use of multivitamins with or without folic acid in any amount if a patient regularly consumes the RDA of nutrients from fortified and non-fortified food sources, or is at least willing to do so in the future. Working with a nutritionist can assist in this process, which would represent a reasonable "first, do no potential harm" approach until this controversial issue is resolved.

Selenium and/or vitamin E. SELEBLAT (Selenium and Bladder Cancer Trial), a phase III trial of 200 mg selenium daily compared to placebo for 3 years, was conducted at 14 Belgian hospitals.[29] There was no difference between placebo and selenium in the probability of bladder cancer recurrence. In SELECT (Selenium and Vitamin E Cancer Prevention Trial), a phase III trial, selenium and/or vitamin E also failed to demonstrate any benefit, not just for prostate cancer prevention (primary end point), but also for bladder cancer prevention.[30-32] Interestingly a non-significant higher risk of type 2 diabetes and the potential for an increased risk of aggressive prostate cancer were observed in the selenium allocated group that harbored higher baseline selenium levels.[33] Vitamin E was associated with a significant increase in prostate cancer risk in SELECT.[31]

Another phase III placebo controlled trial similar to SELEBLAT and SELECT is currently being conducted in the United Kingdom. SELENIB is investigating chemoprevention using selenium and/or vitamin E in patients with early stage bladder cancer (4 treatment arms).[34] However, it is questionable whether a reduction in bladder cancer recurrence (primary end point) would change clinical guidelines because of the ample past negative phase III data. Additionally SELENIB is listed on clinicaltrials.gov as initiating recruitment in late 2005, which suggests recruitment issues and/or less than unequivocal results. Regardless, lifestyle data and disease recurrence information garnered from this and other studies could be substantial, and pooled observations from SELEBLAT and SELENIB should be of interest along with comparing and contrasting other phase III trials of these interventions. Clinicians should remind patients that selenium and vitamin E are adequately provided in healthy foods, and minute amounts are needed for maximum efficacy.

Promising probiotic or another diet and lifestyle option? There appears to be intense interest in the area of probiotics for prevention and treatment of numerous cancers and disease states.[35] **Nothing notable has emerged in cancer research except in urology. Preliminary consistent evidence now exists to conduct a rigorous randomized trial with the probiotic Lactobacillus casei strain Shirota as a potential adjuvant treatment for superficial bladder cancer.**

Two small preliminary randomized, controlled, double-blind investigational trials were conducted in patients with superficial transitional cell carcinoma of the bladder to determine the impact of 3 gm LcS powder orally per day on recurrence after transurethral resection. Study 1 randomized 23 subjects to LcS and 25 to placebo,[36] while study 2 allocated 61 patients to LcS and 64 to placebo.[37] While the 2 groups in study 1 had similar clinical baselines, the 50% recurrence-free interval after LcS treatment was 1.8 times longer compared to placebo (350 days vs 195 days, p=0.03).[36]

Study 2 allocated patients to 1 of 3 subgroups according to tumor baseline status.[37] Cases of multiple primary tumors, single recurrent tumors and multiple recurrent bladder tumors were included in subgroups A, B and C, respectively. The 50% recurrence-free interval in subgroups A and B was longer with LcS vs placebo (688 vs 543 days), while no significant difference was noted in subgroup C. Multivariate analysis indicated that the outcomes with LcS were significantly better compared to placebo (p=0.01). Mild diarrhea was the primary side effect in 3 participants (4.6%) taking LcS and none required treatment. These preliminary observations suggest that LcS has an attractive short-term safety profile and could potentially have a role in preventing or prolonging onset of recurrence of superficial bladder cancer in select patients, although more clinical data are needed.

In a trial of LcS 207 patients diagnosed with superficial bladder tumors were randomized after resection to epirubicin alone or epirubicin and 3 gm LcS orally per day for 1 year.[38] A significantly greater 3-year recurrence-free survival rate was noted in the probiotic combination group vs those taking epirubicin alone (74.6% vs 59.9%, p=0.02). There was no difference in progression-free or overall survival, although this could have been due to the small number of clinical events.

Laboratory research has suggested an enhanced systemic and localized immune response against bladder tumors with LcS.[39-43] This probiotic could activate natural killer cells or lymphocytes, or induce direct cytotoxicity. It is also interesting that the beverage Yakult (Yakult Honsha, Tokyo, Japan), a fermented milk product, contains this same patented probiotic strain, and this strain and similar bacteria from cultured milk may be associated with a reduced risk of bladder cancer based on several previous epidemiological studies.[44-46] LcS could also simply reduce carcinogenic exposure durations or contact time with the bladder itself.

Unfortunately, the momentum of LcS in bladder cancer research has not continued. Whether from funding issues, lack of interest or even unpublished data, one can only speculate why this product has not received more attention since it represents one of the only supplements with consistent preliminary positive data in patients with bladder cancer. The probiotic agent used in prior studies did not have to be refrigerated, which also seems advantageous. The product was powdered and contained approximately 1×10^{10} cells of heat killed LcS strain per gram (3000 mg or 3 gm daily). Although Yakult appears to be an option for patients, the company does not currently provide this delivery system globally.

Yakult has been on the market for more than 50 years in Japan and Taiwan, and has a well-known safety record even when used daily for up to 4.5 years. It is classified as a "generally recognized as safe" additive by the FDA.[47] One Yakult light beverage has 30 calories, and contains a smaller percent-

age (approximately 20% to 25%, depending on standard size marketed in different countries) of the daily amount of the patented probiotic used in clinical trials. Thus, 1 drink (65 to 80 ml, or less than 3 ounces) daily would provide some exposure to this agent, although without more research it is unknown whether this amount is adequate. This beverage is also a fermented dairy product containing small amounts of lactose, so those with moderate to severe lactose intolerance are poor candidates. Regardless, issues with dairy should be discussed with the physician. Patients should also be informed that this product has not been tested in a clinical study during or following treatment with bacillus Calmette-Guérin. This status creates an opportunity for another clinical trial of this specific probiotic beverage.

Often missed in the debate over probiotics and what supplement to ingest or not is the ongoing research suggesting that healthy lifestyle changes increase the probability of creating a more optimal microbiome environment.[48] Smoking cessation, healthy weight and a plethora of other heart healthy changes including greater fiber intake appear to maximize gut health without the initial need for a probiotic agent. Patients should be educated on the power of lifestyle changes to function as a prebiotic that continuously creates or encourages an advantageous microbiome.

B12 deficiency. Another supplement issue is the potential for vitamin B12 deficiency due to the mean age of patients with bladder cancer, use of multiple common medications that reduce absorption, strict plant based diets and the increased risk with cystectomy (continent urinary diversion).[49,50] NCCN® (National Comprehensive Cancer Network®) guidelines recommend following annual B12 levels postoperatively in patients since studies have indicated a risk of deficiency as it is primarily absorbed in the ileum.[50] One baseline or preoperative B12 test in patients with bladder cancer should also be added to NCCN guidelines to compare and contrast its natural progression from before to after surgery. Such a test would improve intervention guidance in less overt cases.

Supplementation of B12 only (no other added B vitamins), if needed, is cost-effective. B12 deficiency is unique among laboratory tested nutrients due to the potential range of individual and multiple medical conditions associated or mimicked when it occurs. B12 deficiency can present asymptomatically or as glossitis, altered mental status, cognitive defects, infertility, myelopathy, megaloblastic anemia and even life threatening pancytopenia. Preliminary research suggests a potential reduced risk of bladder cancer with a diet higher in B12, which could be a reflection or marker of health status.[51,52] Once again, an opportunity to clinically emphasize healthy dietary options of B12 presents itself within the data on pill use, which continues to represent patient empowerment and control.

Gum chewing supplementation. Another notable supplement topic is the preliminary interesting data suggesting that gum chewing after cystectomy reduces prolonged ileus and improves bowel motility as well as time to flatus and first bowel movement.[53,54] Protocols have generally used sugar-free gum chewing for 30 minutes 3 times daily, at 10 a.m., 3 p.m. and 8 p.m., or chewing 1 piece every 2 to 4 hours beginning on postoperative day 1 until discharge home. Studies have suggested that gum chewing is well tolerated with minimal issues. Regardless, individuals should be evaluated on a case by case basis and it is suggested that, if able, they chew while in an upright, sitting or standing position to reduce risk of asphyxiation. This is a simple cost-effective and patient empowering form of IM.

More lifestyle changes (more is more). Tobacco use is associated with more aggressive features at presentation, higher risk of recurrence, less than efficient response to intravesical therapy, and higher bladder cancer and all-cause mortality rates.[55,56] **Multiple other lifestyle recommendations have received minimal attention in comparison but could also be proffered throughout the bladder cancer risk reducing spectrum because they also have the potential to impact all-cause mortality.** Preliminary evidence suggests that exercise reduces bladder cancer mortality,[57] and the profound potential impact on diverse mental and physical health and wellness is sufficient to prescribe regular activity of any type, including resistance, aerobic and meditative forms (qigong, tai chi, yoga), to all patients.[58,59] The specific impact on cancer related fatigue above that observed even with pharmaceutical interventions has recently been noted. Obesity may also be associated with an increased risk of progression and bladder cancer mortality,[60] and reducing other heart unhealthy behaviors should be encouraged, including improving general dietary quality for overall health. Improved overall health behavior reduces the need to review the ambiguous data surrounding other items such as fruit and vegetable consumption in patients with bladder cancer and instead places the focus on the more unambiguous data to improve all-cause mortality.[61] Water consumption in terms of quality, or clean water sources low in heavy metals, could become more of an emphasis in terms of bladder cancer vs quantity of water consumed, which is controversial. Encouraging patients to test private water sources for arsenic is a productive suggestion based on past and current data.[62]

PROSTATE CANCER: LESS IS ALSO MORE, EXCEPT WITH LIFESTYLE CHANGES

IM advice for prostate cancer cases generally mirrors that for bladder cancer in terms of supplements, which have demonstrated either no impact in phase III clinical trials or a risk of detriment. These observations are generally derived from primary vs secondary prevention trials, which should be of minimal emphasis since any agent that potentially encourages prostate cancer growth should not be recommended throughout the spectrum of prostate cancer treatment. In VITAL (Vitamin D and Omega-3 Trial), a recent phase III clinical trial (25,871 patients) for primary prevention, vitamin D and fish oil also failed to reduce the risk of cardiovascular disease and cancer (primary end points) including prostate cancer,[63] although longer follow-up data are needed from this and other trials. These agents did not significantly increase the risk of cancer at their respective dosages, which is also noteworthy. Interestingly in this study being of a healthier weight may have been advantageous against cancer when supplementing with vitamin D, although this issue needs more research. There was a 12% non-significant increase in kidney stone risk with 2000 IU vitamin D (RDA is 600 to 800 IU), which may or may not be relevant after more data are garnered. In the Women's Health Initiative phase III trial (36,282 patients) 400 IU vitamin D with a calcium carbonate supplement appeared to be responsible for a 17% increased risk of kidney stones.[64] For example, it is theoretically probable that as more vitamin D or calcium is added to the food supply, even lower supplement dosages could tip the balance in patients with idiopathic hypercalciuria.

Again, this finding is speculative but noteworthy and needs more investigation, especially while the current nephrolithiasis epidemic continues.

Multivitamins (1 daily) have not demonstrated a reduction in bladder or prostate cancer in the phase III PHS2 (Physicians' Health Study II) but there was a modest reduction in total cancer risk.[65] Suggestions of an increase in aggressive or fatal prostate cancer in men taking more than 1 multivitamin daily, including those with a family history or who took other additional supplements (beta-carotene, selenium or zinc), need more research.[66] The additional concern expressed about folic acid supplementation (not dietary sources) and bladder cancer also exists from prior and recent prostate cancer research.[67, 68]

Vitamin C supplementation showed no benefit in reducing total cancer risk in PHS2, or bladder or prostate cancer prevention.[69] No benefit and a suggestion of concern (more trials are currently ongoing) were indicated in a recent small trial of intravenous vitamin C in patients with advanced prostate cancer.[70]

Vitamin E and selenium represent the most phase III evidence that more of an IM supplemental agent is not tantamount to a benefit in primary cancer prevention. In fact, studies of patients with prostate cancer taking these supplements suggest the potential for an increased risk of progression or mortality, for example with higher selenium dosages.[71] Appendix 4 (online issue only) is a summary of supplements with phase III and epidemiological data on bladder and prostate cancer.

It should be explained to patients that these findings do not suggest that selenium, vitamin E or any other supplement has no potential positive role in medicine. They are used in different specialties for conditions such as Alzheimer disease and non-alcoholic steatohepatitis, or as part of a mixed supplement which includes vitamin E for age related macular degeneration (AREDS trial).[20] Supplements are a part of many diverse clinical guidelines. In oncology they have the potential to mitigate or amplify the side effects of treatment,[72] or even interfere (eg biotin) with some oncologic assays.[73] Regardless, most of the positive data in oncology are still derived from lifestyle changes (aerobic and resistance exercise, diet).

Heart healthy lifestyle changes have been tantamount to prostate healthy changes, which include virtually every major cardiovascular parameter from blood pressure to cholesterol, glucose, weight, waist circumference and even inflammation.[74] Interestingly even heart healthy generic preventive drugs derived from "natural sources" (statins, aspirin, metformin) are currently being evaluated in a plethora of clinical trials across the prostate cancer prevention and treatment spectrum. Appendix 5 (online issue only) contains a summary of lifestyle changes that can be encouraged in patients with bladder or prostate cancer.

CONCLUSION

Patient empowerment, or an attempt to harbor some level of control over a difficult and humbling condition, is a primary reason proffered as to why IM options, especially supplements, are attractive. **However, an opportunity to gain some sense of control by patients currently exists since lifestyle changes are a form of intrinsic empowerment that does not whisper but shouts after countless clinical studies.** All urological health care professionals (clinicians, dieticians, pharmacists) should be unified in their collective enthusiasm over what patients can currently be instructed to accomplish for themselves and regain some of this much needed control and confidence. The evidence is profound. Educating and motivating patients to consistently adhere to heart healthy lifestyle changes could impact the cancer itself while simultaneously improving all-cause morbidity and mortality. This outcome is one of the most beautiful aspects of evidence-based conventional medicine and complementary IM.

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Study Questions Volume 39 Lesson 2

1. The most consistently used IM intervention in patients with cancer is
   a. meditation
   b. acupuncture
   c. chiropractic care
   d. dietary supplements

2. Quality control guidance for dietary supplements is provided by
   a. Safe Shield
   b. NSF International
   c. Nutraceutical choice labs
   d. United supplement labs

3. Bladder and prostate cancer incidence or recurrence may be increased by high (mega) doses of
   a. beta-carotene
   b. folic acid
   c. vitamin C
   d. vitamin D

4. The most recent NCCN guidelines for patients after cystectomy (urinary diversion) advise monitoring and potentially supplementing with
   a. vitamin B1
   b. vitamin B2
   c. vitamin B6
   d. vitamin B12

5. Two phase III clinical trials (SELECT and SELEBLAT) demonstrated no impact on the incidence of prostate cancer or the recurrence of bladder cancer by taking
   a. beta-carotene
   b. selenium
   c. vitamin C
   d. vitamin D

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