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# Multivitamin Use may Improve Disease-free and Distant Metastasis-free Survival in Patients with Soft Tissue Sarcomas of the Extremity and Chest-wall

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## Abstract

**Introduction:** Multivitamins (MVT) are used for their potential benefit by patients diagnosed with cancer. There is a paucity of data correlating their use and outcomes in rarer malignancies. Thus, the aim of this study was to correlate MVT use with survival in patients with soft tissue sarcomas (STS).

**Materials and methods:** Between 2000-2012, 185 patients with stage I-III STS underwent treatment. Variables were retrospectively analyzed relating to overall (OS), disease-free (DFS), and distant-metastasis free survival (DMFS). Univariate analysis (UVA) was performed using the log-rank test. Multivariate analysis (MVA) was performed using the Cox proportional hazards model.

**Results:** Median follow-up was 3.6 years. 34% had record of taking a MVT at the time of diagnosis. Of these, 10% developed metastasis compared to 39% who were not taking a MVT at the time of their diagnosis.

On UVA, MVT was associated with an improved DFS ($p=0.001$) and DMFS ($p=0.001$). On MVA for DFS and DMFS, smoking ($p<0.01$), stage III tumors ($p<0.01$), and statin use ($p<0.01$) were negative predictors, however MVT use ($p<0.001$ was associated with improved DFS and DMFS.

**Conclusions:** Patients taking a MVT at the time of diagnosis had improved DFS and DMFS in our cohort. This may suggest that MVT use prevents distant metastasis.

**Keywords:** Soft tissue sarcomas; Multivitamin; Supplements; Survival

## Abbreviations

STS: Soft Tissue Sarcomas

MVT: Multivitamins

IRB: Institutional Review Board

AJCC: American Joint Committee on Cancer

IMRT: Intensity Modulated Radiation Therapy

Gy: Gray

GTV: Gross Tumor Volume

CTV: Clinical Target Volume

PTV: Planning Target Volume

KPS: Karnofsky Performance Status

MVA: Multivariate Analysis

DFS: Disease Free Survival

DMFS: Distant-Metastasis Free Survival

OS: Overall Survival

## Introduction

Environmental factors and lifestyle changes such as smoking cessation and dietary fat intake play an important role in many cancers. Many vegetables and supplements are treated as having anti-cancer properties. Nevertheless, there is little objective research documenting the decreasing the risk of recurrence and improving outcomes in patients with soft tissue sarcomas (STS) or other rare malignancies.

Multivitamins (MVTs) are the most common dietary supplement used in the United States, with a reported 33% of the US population using multivitamins-multi-mineral dietary supplements, and 14% to 32% of adults using supplements after a cancer diagnosis [1].

Advantages of MVTs include inhibition of cell proliferation, apoptosis, and angiogenesis [1,2], however there has been a paucity of data correlating MVTs or multi-minerals supplement use of outcomes including control and survival of disease. Vitamin D intake has been shown in some studies to be beneficial in patients with

adenocarcinoma of the prostate [3-13]. Increased Vitamin D3 levels have been shown to be associated with decreased aggressiveness and decreased percent of positive cores on biopsies in patients with prostate cancer [13-14]. Kwan, et al. demonstrated a non-significant decrease in the risk of recurrence and total mortality in breast cancer patients who consistently used MVTs from pre to post-diagnosis of their disease [15]. Although limited correlation data exist between evaluating supplement use and more common malignancies, there has been no reported association with rarer cancers, such as soft tissue sarcomas.

Multivitamins are one of the most common supplements taken from the general population. Many studies have demonstrated benefits of individual vitamins and minerals as well as multivitamins, such as decreased proliferation and induction of apoptosis.

The 2010 Dietary Guidelines for Americans [16] and National Institute of Health-State of the Science Conference both determined, however, that there was a lack of evidence supporting or refuting the use of multivitamins to prevent disease. Yet, many patients still use vitamins and minerals to prevent such chronic diseases, particularly cancer. As such, it is imperative to determine if supplements and minerals impact the development or progression of cancer, as it affects decision-making for both the patient and their care givers.

In this study, we aim to investigate the correlation between MVT, single-supplement use, medications and lifestyle factors to overall, disease-free and distant metastasis-free survival in patients with soft tissue sarcomas. It is known that supplements and minerals may impact non-malignant and malignant processes, but there is little data in the setting of rare tumors, such as soft tissue sarcomas. Thus, we propose to assess the impact of mineral and supplement use in patients with soft tissue sarcomas in terms of disease control and survival.

The outcome of this study may be meaningful, as many cancer patients use supplements and minerals in addition to the prescribed therapies by their physician, in hopes of improving not only their overall health status, but also combating the malignancy itself.

## Materials and Methods

This research was reviewed and approved by the Institutional Review Board (IRB) and all investigators completed training in both human research and patient privacy.

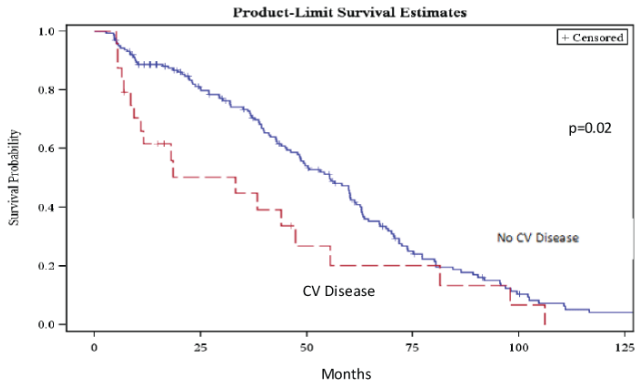


**Figure 1a:** Cardiovascular disease and overall survival (All patients).

All records of patients with localized primary STS of the upper extremity, lower extremity, and body-wall who underwent multimodality treatment with surgical resection, radiation, and/or chemotherapy between May 2000 and 2012 were reviewed. Exclusion criteria included STS of locations other than the extremity or body-wall, patients who presented with metastasis or recurrent sarcomas, and histopathologic type rhabdomyosarcoma, extraosseous primitive neuroectodermal tumor, Ewing's sarcoma, osteosarcoma, Kaposi's sarcoma, angiosarcoma, aggressive fibromatosis, or dermatofibrosarcoma protuberant, solitary fibrous tumor and follow-up less than 6 months. Patients who only received primary surgical intervention at this institution and were not followed for their metastatic disease were excluded from this analysis. One hundred and eighty-five patients were identified in our database who met the inclusion criteria. Patients were staged according to the 2009 American Joint Committee on Cancer (AJCC) system seventh edition. Patients at the institution were staged and monitored with the following protocol.

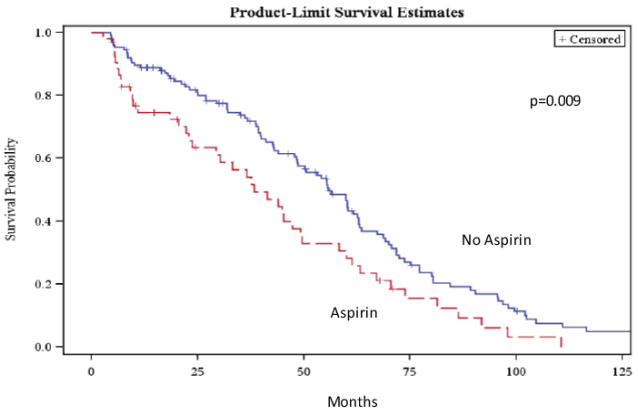


**Figure 1b:** Aspirin and overall survival (All patients).

An MRI of the primary site and a PET/CT scan if insurance approved, or a CT of the chest, abdomen, or pelvis was obtained for initial staging. Once therapies were completed, surveillance included a CT of the chest, abdomen and pelvis every 4 months for intermediate to high grade lesions for 2 years followed by every 6 months for an additional 3 years. For low grade lesions, patients received either CT of the chest, abdomen and pelvis every 6 months or a chest x-ray, depending on patient preference, for 5 years.

All patients were discussed at a multidisciplinary tumor board consisting of surgical and orthopaedic oncologists, medical and radiation oncologists, radiologists and pathologists. Treatment recommendations from this tumor board were presented to the patient.

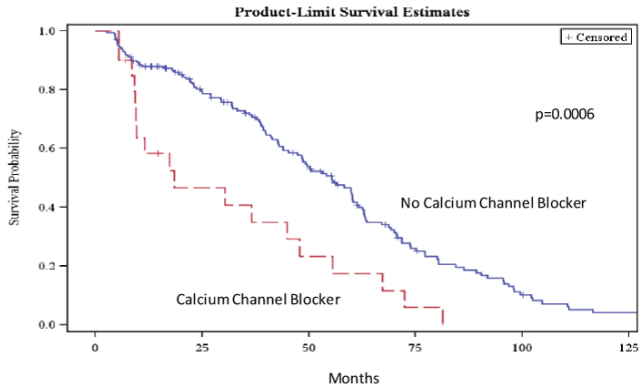


**Figure 1c:** Calcium channel blocker and overall survival (All patients).

### Radiotherapy and chemotherapy

Patients received a median dose of 50 Gy using 3D-conformal radiation or intensity-modulated radiotherapy (IMRT). The clinical target volume (CTV) was created by adding a 3 cm margin superior and inferiorly and 1-1.5 cm radially to the gross tumor volume (GTV). The planning target volume (PTV) was created by adding a 5 mm margin to the CTV. Tumor volumes were calculated from CT simulation data, and when available, from an MRI acquired in the treatment position.

Chemotherapy was recommended and administered in patients who were typical <70 years of age, with large (>5 cm), deep, and high-grade lesions. Chemotherapy was delivered prior to radiation therapy, using adriamycin and ifosfamide for 2-3 cycles.

### Surgery

Limb-sparing resection was performed in all patients either as the sole management or 4-6 weeks after radiotherapy. Wide surgical resection was performed by fellowship trained musculoskeletal oncologists grossly through normal tissue planes with sacrifice of arteries or veins that were involved by tumor. Preservation of neurovascular structures was performed when possible. The goal of surgery was to achieve negative margins (R0). Vascular or reconstructive plastic surgeons were involved in cases that required vascular reconstruction, difficult wound closures and free flap reconstructions.

### Supplement and medication use

Data was obtained through medical records and included information on patient and tumor characteristics, past medical history, medication use, and dietary supplement use. MVT use was defined as patients taking a multivitamin supplement that contained various supplements. Patients were not considered as MVT users if they took multiple supplements independently. Information on supplement use included patients taking MVT, vitamin B, C, and D, folate, chromium, cinnamon, glucosamine chondroitin, calcium, Omege-3 fatty acid, and zinc at the time of their diagnosis. Patient medication and supplement usage and frequency was determined at each visit by medical personnel and those who were not taking the above supplements at the time of their diagnosis were recorded as non-users.

### Statistical analysis

Prognostic factors for overall (OS), disease-free (DFS) and distant metastasis-free survival (DMFS) in those patients that developed metastatic disease were analyzed, including age, performance status using the Karnofsky Perfomance Scale (KPS), patient comorbidities, medication use, histologic type and grade, tumor stage, location, and size, and treatment characteristics (Appendix 1). Groups were compared by the log-rank test and multivariate analysis (MVA) was performed using the Cox proportional hazards model. The tests were two-sided. The proportional hazards assumption was tested and was never violated at a p-value of 0.05. This was an exploratory analysis and no adjustments for multiple comparisons were made.

## Results

### Patients characteristics

One hundred and eighty-five patients with stage I-III STS of the extremity and body-wall underwent treatment at this institution. The median age at diagnosis was 57 years-old (range 18-92). The median follow-up was 3.6 years. Sixty-six (36%) patients had a history of smoking, as defined by a ≥10 pack-year history of smoking. Clinical and pathologic characteristics of patients and tumors are located in Appendix 1.

### Tumor characteristics

All patients had STS of the extremity or body-wall. Thirty (16%) patients had tumors located in the upper extremity, 14 (8%) had body-wall, 111 (60%) had proximal lower extremity, and 30 (16%) had distal lower extremity tumors. The most common histology was leiomyosarcoma or liposarcoma (33%). One-hundred and twenty-seven (69%) patients had high grade tumors.

### Medication and supplement use

Medications, MVT and individual supplements use were defined as those patients taking these substances at the time of diagnosis and continued use through diagnosis and in follow-up for at least one year. Medical personnel inquired about these substances at each visit to ensure the accuracy, frequency and compliance of usage prior to each clinic visit. Physicians would also review medication, MVT and supplement profile and inquire about patient administration if warranted.

The most common medication used by patients in this study was aspirin, which was taken by 29% of patients. The most common supplement taken was a MVT, which was taken by 34% of patients once daily (Appendix 2). Comparison of patient and disease characteristics between MVT and non-MVT users is located in Tables 1 and 2. There were no differences in disease attributes between MVT and non-MVT users, however, patients were taking MVTs were more likely to take other supplements as well.

| Patient Traits | Non-MVT Users (%) | MVT Use (%) | p-value |
|---|---|---|---|
| Gender | M: 61 | M: 49 | 0.15 |

| | | | |
|---|---|---|---|
| | F: 39 | F: 51 | |
| Age | <70: 77.8 | <70: 62.3 | 0.03 |
| | ≥ 70:22.2 | ≥ 70: 37.7 | |
| KPS ≥ 80 | 85.5 | 78.7 | 0.31 |
| Diabetes | 12.8 | 8.2 | 0.5 |
| Cardiovascular Disease | 11.1 | 14.8 | 0.5 |
| Smokers | 38.5 | 31.1 | 0.4 |
| Metformin User | 4.3 | 8.2 | 0.31 |
| ASA User | 24.8 | 37.7 | 0.08 |
| Prednisone User | 0.08 | 5 | 0.12 |
| Calcium Channel Block Users | 11.1 | 11.5 | 1 |
| Cox-2 Inhibitor | 0.08 | 7 | 0.05 |
| Statin User | 22.2 | 27.8 | 0.46 |
| Vitamin D User | 10.3 | 50.8 | <0.0001 |
| Vitamin C User | 1.7 | 14.7 | 0.001 |
| Vitamin B User | 5.2 | 9.8 | 0.34 |
| Folate User | 1.7 | 4.9 | 0.34 |
| Chromium User | 1 | 1.6 | 1 |
| Cinnamon User | 1 | 3.3 | 0.27 |
| Glucosamine User | 2.6 | 11.5 | 0.03 |
| Calcium User | 3.4 | 29.5 | <0.001 |
| Omega-3 User | 7.6 | 21.3 | 0.01 |
| Zinc User | 0 | 4.9 | 0.04 |
| Supplements other than MVT | 25 | 75.4 | <0.001 |

**Table 1:** Comparison patient factors between MVT and Non-MVT users.

## Treatment characteristics

All 185 patients underwent limb-salvage resection. No patient underwent an amputation at the time of definitive resection; however, one patient had an amputation for an associated failed infected bone reconstruction with vascularized flap.

| Disease Traits | Non-MVT Users (%) | MVT users (%) | p-value |
|---|---|---|---|
| Histology | Undifferentiated 21.0 | Undifferentiated 27.9 | |
| | Leiomyosarcoma/ Liposarcoma 33 | Leiomyosarcoma/ Liposarcoma 32.8 | 0.92 |
| | Myxofibrosarcoma 9.7 | Myxofibrosarcoma 22.9 | |
| | Other 36.3 | Other 16.4 | |
| Grade | 64.5 | 68.8 | 1 |
| Location | Upper Extremity 23.4 | Upper Extremity 26.2 | |
| | Proximal Lower Extremity 62.9 | Proximal Lower Extremity 54.1 | 0.63 |
| | Distal Lower Extremity 13.7 | Distal Lower Extremity 19.7 | |
| Stage | I: 17.7 | I: 11.5 | |
| | II: 20.2 | II: 36.1 | 0.66 |
| | III: 62.1 | III: 52.4 | |
| Chemotherapy | 32.3 | 36 | 0.87 |
| Radiation | 88.7 | 86.9 | 0.62 |
| Tumor Size ≥ 5 | <5 cm: 16.1 | <5 cm: 24.6 | 0.1 |
| | ≥ 5 cm: 83.9 | ≥ 5 cm: 75.4 | |

**Table 2:** Comparison of disease factors between MVT and Non-MVT users.

One hundred and forty (76%) patients underwent preoperative, 23 (12%) patients had post-operative radiation, and 22 (12%) patients did not receive any radiation therapy, either in a neoadjuvant or adjuvant setting. Fifty-five (30%) patients received neoadjuvant chemotherapy. Chemotherapy was a doxorubicin-ifosfamide based regimen given for 1 to 3 cycles based on clinical response. Adjuvant chemotherapy was administered in 18 patients (10%), with 11 patients receiving doxorubicin and ifosfamide, 2 patients receiving epirubicin and ifosfamide, 1 patient receiving ifosfamide and etoposide, and 4 patients receiving an unknown regimen at an outside institution.

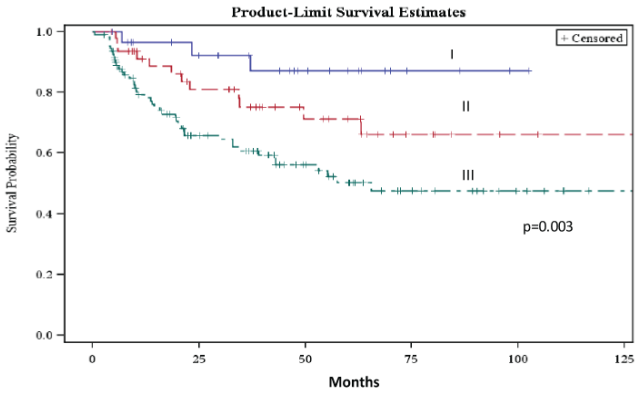


**Figure 2a:** Stage and disease-free survival (All patients).

## Clinical outcomes-overall survival

The overall local control recurrence rate was 3.2% in both groups who used and did not use MVT. Ninety-five percent of patients had R0 resections, with a limb-salvage rate of 99%. Clinical factors that were associated with a decreased OS on UVA included the presence of cardiovascular disease (p=0.02) (Figure 1a). Moreover, decreased overall survival on UVA was seen in patients who routinely used aspirin (p=0.009) and calcium-channel blockers (p=0.0006) (Figure 1b and 1c).

On MVA, aspirin (p=0.03, HR 1.5), and calcium-channel blockers (CCB) (p=0.003, HR 2.1) both predicted for poorer overall survival. Post-hoc analysis, however, revealed that there is a strong association for age and ASA (p=0.0001) and age and CCB (p<0.0001).

### Clinical outcomes-disease-free and distant metastases-free survival

Clinical and pathologic factors that lead to decreased DFS on UVA included the presence of diabetes (p=0.02), stage III disease (p=0.003), high grade lesions (p=0.01), and smokers with a≥10 year pack history (p=0.02).

Clinical and pathologic factors that lead to a decrease in DMFS on UVA included age (p=0.03), stage III disease (p=0.002), tumor size >5 cm (p=0.02), high grade lesions (p=0.04), and smokers with a ≥10 year pack history (p=0.006).

Patients who had a record of taking a MVT prior to, during and after diagnosis and treatments were found to have an increase in DFS and DMFS (p=0.0004) (Figures 2a-2e and 3A-3F). The median DFS and DMFS were not reached in patients taking MVTs; however was 63 months for both DFS and DMFS in those not taking MVTs.

On MVA for DFS, smoking (p=0.008, HR 2.0), stage III tumors (p=0.003, HR 5.9), and HMG-COA reductase inhibitor use (p=0.02, HR 2.10) were negative predictors, however MVT use (p=0.0004, HR 0.25) was associated with improved DFS. On MVA for DMFS, smoking (p=0.002, HR 2.4) stage III disease (p=0.004, HR 5.7), and HMG-COA reductase inhibitor use (p=0.006, HR 2.5) was associated with decreased DMFS and MVT use (p=0.0004, HR 0.23) was associated with improved DMFS.

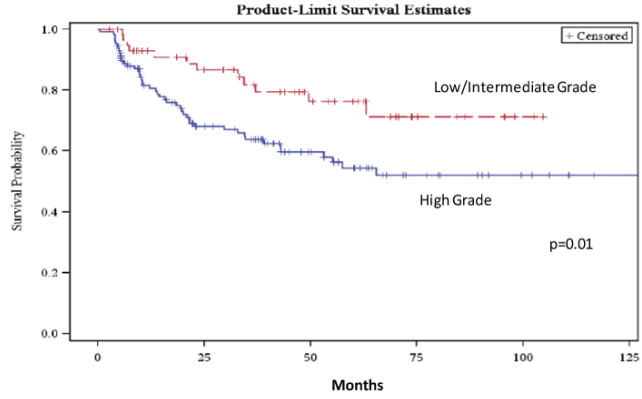


**Figure 2b:** Grade and disease-free survival (All patients).

Post-hoc analysis, revealed that there is a strong association of age and HMG-COA reductase inhibitor use (p=0.0001).

Fifty-five patients (29.7%) developed distant metastasis in this cohort. On UVA and MVA, MVT use (14.1 vs 13.9 mo, p=0.59) nor any other supplement predicted for longer survival once diagnosed with metastatic disease.

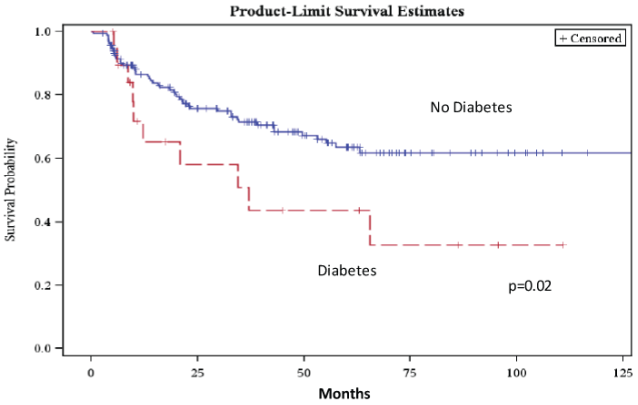


**Figure 2c:** Diabetes and disease-free survival (All patients).

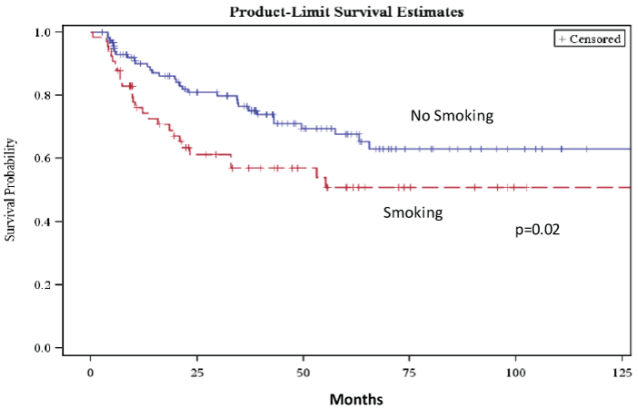


**Figure 2d:** Smoking and disease-free survival (All patients).

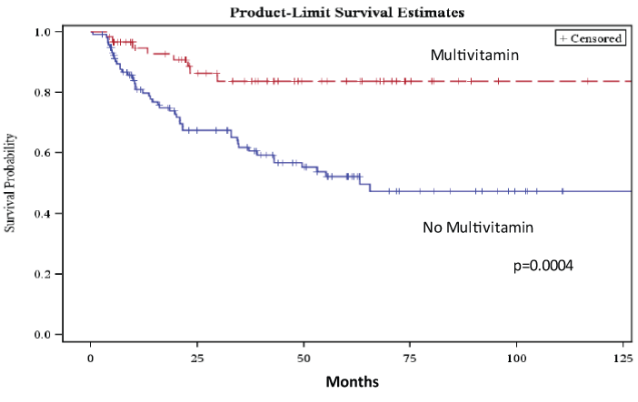


**Figure 2e:** Multivitamin use and disease-free survival (All patients).

## Discussion

Many studies have assessed the impact of supplement or mineral use in cancer prevention; however, there has been little data on the effect of single mineral or multi-mineral use on outcomes such as survival and

control of rare diseases. In this retrospective study, MVT use prior to, during and after diagnosis of STS, was associated with improved DFS and DMFS. To date, this is the only study that has correlated with any clinical outcome of MVT use and STS (Figures 3a to 3f).

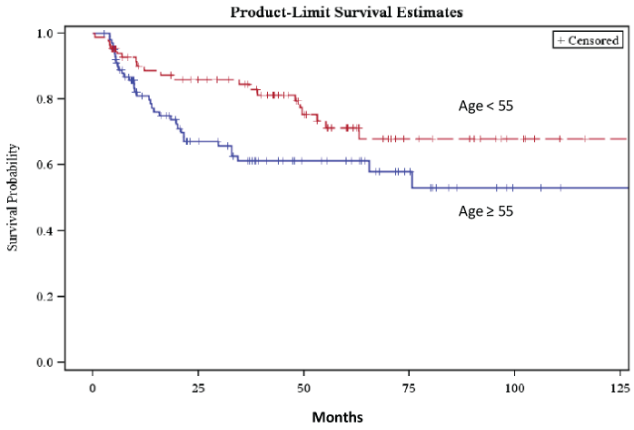


**Figure 3a:** Age and distant metastasis-free survival (All patients).

Perhaps some of the most abundant data on vitamin and mineral use and cancer outcomes is in breast cancer patients [16-24]. Hatse, et al. [19] collected serum from 1,800 patients with non-locally advanced, non-metastatic breast cancer patients and assessed 25-hydroxy vitamin D levels [25] by radioimmunoassay. These levels were correlated with tumor characteristics and outcomes, such as OS, disease-specific survival (DSS), and disease-free interval (DFI). In this study, decreased levels of 25(OH)D were associated with larger tumors at the time of diagnosis (p=0.006) and high levels of 25(OH)D correlated with improved OS (p=0.01), DSS (p=0.02).

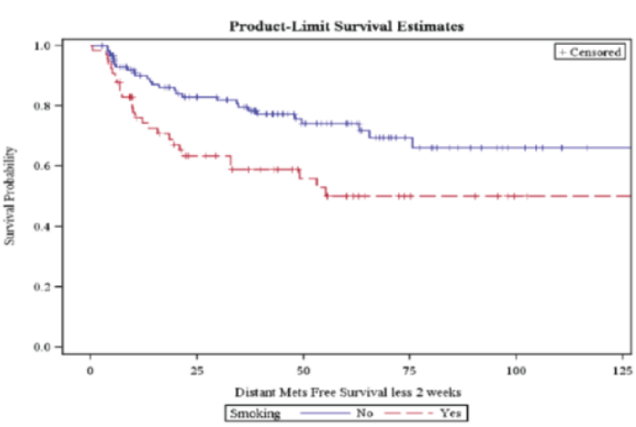


**Figure 3b:** Smoking and distant metastasis-free survival (All patients).

This benefit was seen predominantly in post-menopausal breast cancer patients, where higher (>30 ng/mL) levels were associated with improved DSS (p=0.01) and DFI (p=0.02). This relationship was not demonstrated in pre-menopausal breast cancer patients (19). This association between 25-hydroxy vitamin D levels and post-menopausal breast cancer was also confirmed in a study by Vrieling, et al. [20]. In this prospective study, 1,295 post-menopausal breast cancer patients had their 25(OH)D levels measured and correlated with outcomes. Similarly to Hatse, et al. [19] this study revealed lower concentrations of 25(OH)D levels were associated with increased risk of death and distant recurrence [20].

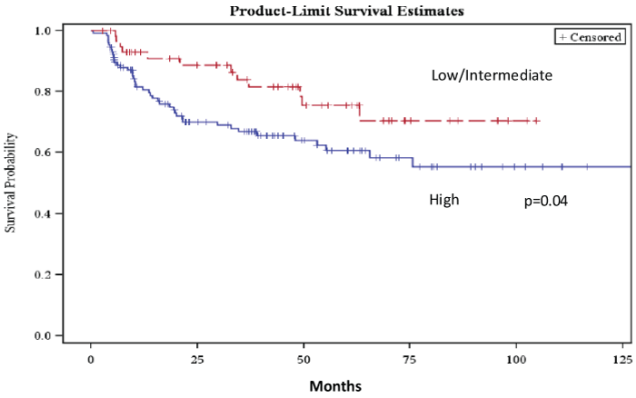


**Figure 3c:** Grade and distant metastasis-free survival (All patients).

MVT use has been investigated in the prevention of breast cancer and has been shown to correlate with clinical outcomes in this patient population [15,18,22-24]. Nechuta, et al., [24] conducted a prospective cohort study of 4,877 females who were diagnosed with invasive breast cancer. In this study, vitamin use, including vitamin E, C, and/or MVT, within 6 months of diagnosis led to a 22% reduction in recurrence (HR 0.78, CI 0.63-0.95) and 18% reduction in mortality (HR 0.82, CI 0.65-1.02) [24].

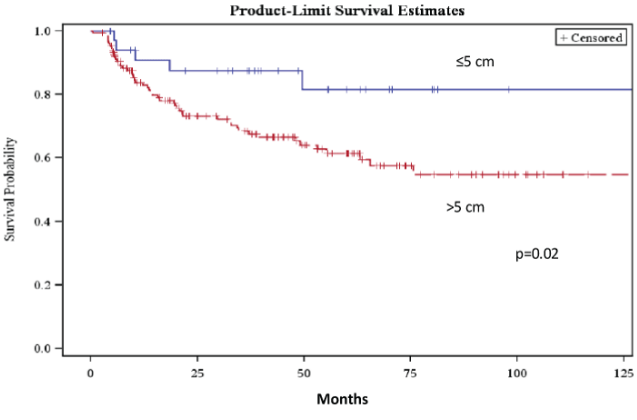


**Figure 3d:** Size and distant metastasis-free survival (All patients).

Similarly, the Life After Cancer Epidemiology Study (LACE) showed persistent use of multivitamins from pre to post-diagnosis was associated with a non-significant decreased risk of recurrence (HR=0.76; CI: 0.54-1.06) and mortality (HR=0.79; CI: 0.56-1.12). This finding was confined to patients who were treated with radiation or radiation and chemotherapy, however [15].

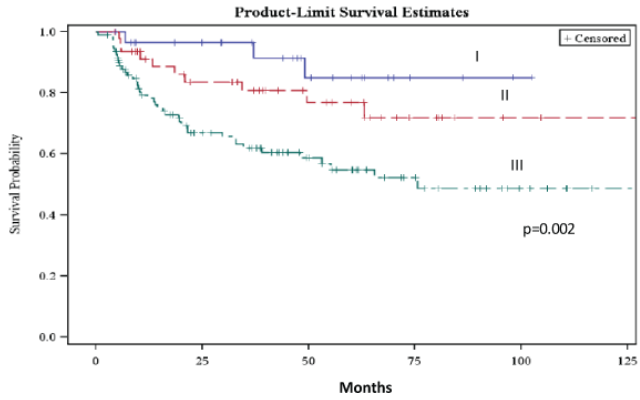


**Figure 3e:** Stage and distant metastasis-free survival (All patients).

Gaziano, et al. [25] conducted a large, double-blinded randomized control trial including 14,641 male US physicians. Patients were randomized to either placebo or daily MVT use. Subjects were ≥50 years of age and a subset of these men had a history of malignancy. In this study, men taking MVT had a reduction in the incidence of total cancer (p=0.04, 95% CI 0.86-0.99), although there was no effect of reduction of prostate, colorectal, or other site-specific malignancies as well as risk of cancer mortality [25].

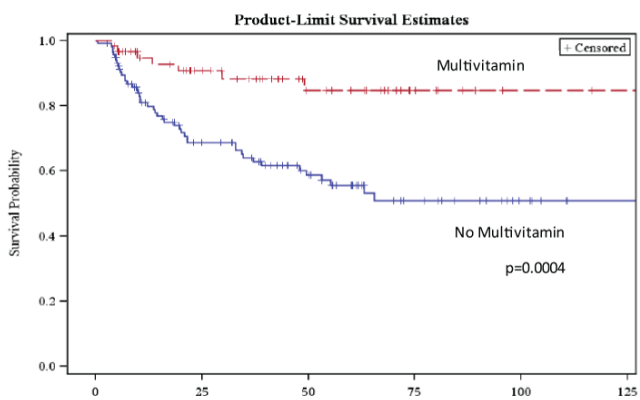


**Figure 3f:** Multivitamin use and distant metastasis-free survival (All patients).

Although there is data on the effect of MVT on various cancer incidences and outcomes other than breast cancer, including prostate, pancreatic, colorectal and esophageal cancer [26-31], there is little other data on MVT use and cancer outcomes in rarer malignancies such as STS. This study illustrates that patients with STS who took a MVT prior to, during and after their diagnosis, had improved DFS (HR 0.25, 95% CI 0.11-0.56) and DMFS (HR 0.23, 95% CI 0.12-0.55) This study not only has revealed the possible benefit of MVT use in another disease site, but also, is the first to show a benefit of any mineral or multi-mineral in patients with STS.

Proposed mechanisms for various vitamins and minerals include, but are not limited to, inhibition of mutagenesis, decreased proliferation, and induction of apoptosis [3,32,33]. Many of the anti-neoplastic properties are felt to arise from anti-oxidants. Although anti-oxidants have been shown to help mitigate treatment related side effects of chemotherapy and radiation, their use is not routinely recommended, as they may counteract the benefits of the production of free radicals by radiation, which cause cell death [34-35]. Although the anti-neoplastic properties of MVT may play a central role in our findings, the possibility exists that MTV use is a surrogate for overall health. However, performance status as measured by KPS, which is an assessment of overall health status, was not correlated with any of the outcomes measured.

It is known that patients who take vitamins and minerals may have an overall healthy lifestyle, and thus the attention to living in accordance to this lifestyle not only incorporates supplement use, but also promotion of diet and exercise. The overall health of the patient and bolstered immune status could account for these findings. In fact, this data does indeed show that patients, who were taking MVTs, were also more likely to take other supplements as well, which could be a proxy for a healthy lifestyle. Although, other confounding variables could not be taken into account when performing this retrospective analysis, other lifestyle and patient factors, such as demographics, smoking status, cardiovascular disease, diabetes, and use of other medications and supplements were taken into consideration.

Lastly, it is well known that supplements and minerals impact the effectiveness of other modalities of therapy. For example, damage produced by radiation is augmented by the use of high doses of nicotinamide, which is the amide derivative of vitamin B3. The mechanism of action is thought to be due to removal of perfusion acute hypoxia [36-37]. Although this supplement has been used in large scale studies with accelerated radiation therapy, the exact dose of nicotinamide needed is not known and the effects on tumor control, particularly in bladder cancer, is not improved compared to historical controls [38-39]. It is feasible in the present study; however, that one particular supplement could enhance the therapeutic effect of radiation or chemotherapy in those that received these treatments.

Other findings of the study showed that patients with stage III disease (HR 5.9, p=0.003) and smokers with a ≥10 pack year history of smoking (HR 2.0, p=0.008) had poorer DFS and DMFS. Although advanced stage has been shown to be prognostic in STS [40-41], smoking has not historically been shown to be prognostic in terms of survival in this disease process.

In this study, aspirin and calcium channel blocker use was associated with poorer OS, and use of HMG-COA reductase inhibitors were associated with poorer DFS and DMFS. However, on post-hoc analysis, each of these drugs was strongly correlated with patient age, such that patients with increasing age were typical users of aspirin, calcium-channel blockers and HMG-COA reductase inhibitors. This correlation did not exist with other supplements or medications, including multivitamin use.

Limitations of this study include its retrospective nature and the inherent biases that correspond to these studies. Moreover, assessment of mineral, multi-mineral or medication use was assessed through electronic medical records alone and there was no verification of compliance of administration of these supplements or medications other that what was indicated in the patient chart and inquiry at the time of follow-up and consultations. Doses and compliance or regularity were inquired by medical assistants, nurses and physicians, however objective measurement of compliance could not be performed. In fact, specific inquiry of unconventional medical

therapies has been investigated. Metz, et al. [42] prospectively evaluated 196 patients using standard history and physical to query unconventional medical therapies. Thirteen patients admitted to using unconventional therapies on standard H&P, however, when asked directly about this therapy, an additional 66 patients admitted to using unconventional medications. Thus, it was determined that directed questioning about unconventional medications leads to an increase in ability to identify the true number of patients who use additional supplements [42]. Also, short follow-up may merely prolong metastatic disease as oppose to limit it.

A prospective study incorporating other overall health and lifestyle influences in addition to more detailed reporting of MVT would potentially shed further light on variables that influence metastasis-free survival of sarcoma patients.

## Conclusion

Patients who were taking a MVT at the time of diagnosis and during and after their treatment for their STS had improved DFS and DMFS in our patient cohort. Patients who developed metastasis and were on an MVT at the time of their initial diagnosis did not have improved metastatic survival compared to those who were not on an MVT. This may suggest that MVT use prevents or prolongs the development of distant metastasis, but does not prolong progression of the disease once one develops metastasis. Further studies, including those of a prospective nature, are needed to corroborate these findings.

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## Competing Interests

The authors' have no disclosures or competing interest pertaining to this study.

## Authors' Contributions

This research was supported in a concerted effort between all authors. All authors contributed equally and they all read and approved the final version of this research article.

## Ethical Approval

This research was reviewed and approved by the Institutional Review Board (IRB) and all investigators completed training in both human research and patient privacy.

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