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Supplement Use and Risk of Cutaneous Squamous Cell Carcinoma

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Abstract

BACKGROUND—Laboratory and epidemiologic studies suggest that certain dietary supplements may alter risk of cutaneous squamous cell carcinoma (SCC).

OBJECTIVE—To examine the association between supplement use and SCC risk.

METHODS—Cases (n= 415) were defined as Kaiser Permanente Northern California (KPNC) members with a pathology-verified SCC in 2004 and controls (n=415) were age, gender, and race-matched members with no previous history of skin cancer. Supplement use and SCC risk factors were ascertained by questionnaire. Associations of SCC with use of multivitamins, vitamins A, C, D and E, and grape seed extract were estimated as odds ratios (OR) and 95% confidence intervals (CI) using conditional logistic regression. Models were adjusted for SCC risk factors and other supplement use.

RESULTS—Grape seed extract users had a significantly decreased risk of cutaneous SCC (adjusted OR = 0.26, CI: 0.08-0.89, p=0.031). Multivitamin use was associated with a borderline significant reduction in SCC risk (adjusted OR = 0.71, CI: 0.51-1.00, p= 0.049). Use of vitamins A, C, D, and E was not associated with SCC risk.

LIMITATIONS—The data may be prone to recall and selection bias due to the case-control design. No information was obtained on dose or duration of supplement use.

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CONCLUSIONS—Use of grape seed extract may be associated with a decreased risk of cutaneous SCC. The other supplements included in our study did not reveal clear associations with SCC risk.

Keywords

Antioxidant; Skin cancer; Squamous Cell Carcinoma; Supplement; Vitamin; Epidemiology

INTRODUCTION

Vitamins, including vitamins A (retinol), C (ascorbic acid), D (califerol), and vitamin E (tocepherol) have been shown in both in vitro and in vivo studies to prevent oxidative damage to keratinocytes,[1,2] suggesting a putative role in the chemoprevention of keratinocyte-derrived carcinomas, including squamous cell carcinoma (SCC).[3,4] Certain herbal supplements, including polypodium leucotomos, derived from a tropical South American fern, and grape seed extract, derived from the seeds of grapes (*Vitis vinifera*), have also been associated with photoprotective effects[5,6] as well as a reduction in cutaneous carcinogensis in laboratory settings.[7,8,9-11] Grape seed extract (GSE) is a rich source of proanthocyanidins and polyphenolic antioxidants which are potent free radical scavengers[12,13] and are postulated to mediate their chemopreventive effects by upregulating Bcl-2 and IL-12, and down regulating 1L-10 production, c-myc, p53, and the expression of NF-kappa B-targeted genes.[6,12] GSE has been shown to have potent anticarcinogenic activity in keratinocytes,[9] in skin carcinoma cell lines, [10], and in mouse models.[11] Although laboratory evidence supports the hypothesis that boosting endogenous antioxidants through oral intake can reduce cutaneous carcinogenesis,[14-16] epidemiologic studies have failed to show a consistent chemoprotective effect of oral supplement use and risk of cutaneous SCC.[17,18] In fact, a recently published randomized controlled trial of nutritionnally appropriate doses of antioxidant supplements implicated a harmful effect of supplements on overall skin cancer risk.[19]

We conducted a case-control study to investigate whether supplement use is associated with SCC risk using the Kaiser Permanente Northern California (KPNC) population. KPNC electronic records include a comprehensive pathology database through which cutaneous SCCs can be accurately identified. We used a self-administered questionnaire to ascertain SCC risk factors and exposure to 7 vitamin and herbal supplements over the 10 years preceding the diagnosis date. These supplements were selected *a priori* based on data in the literature suggesting an association between their use and SCC risk.[4,6,20,21] Our aim was to test whether supplements that have been previously shown to be associated with reductions in photo-oxidative damage in laboratory studies were associated with a reduction in SCC risk.

METHODS

Study Population

Data were derived from a case-control study designed to examine the association between non-steroidal anti-inflammatory drug (NSAID) use and SCC risk.[22] The study population consisted of a random representative sample of 415 KPNC members (ages 43 to 85) with a pathology-confirmed squamous cell carcinoma diagnosed in 2004 and 415 control subjects matched to cases by year of birth, sex and self-reported race.

Subjects were excluded if (1) their spoken language was not English (to maximize questionnaire comprehension), (2) they had a membership gap > 4 months between January 1995 to December 2004, (3) they had a diagnosis of dementia within 10 years prior to SCC

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diagnosis (4) they were age > 85 years, or (5) they had a history of organ transplantation. Each participant was contacted by mail, informed about the overarching goal of the study ("to identify factors that can cause and help prevent skin cancer"), and after informed consent was obtained, asked to complete a self-administered questionnaire inquiring about demographics, skin cancer risk factors, health habits, and exposure to select drugs (NSAIDs) and supplements. This study was approved by the Kaiser Foundation Research Institute Institutional Review Board (CN-05MAsga-01-H, approved January 10, 2006) and was conducted according to the Declaration of Helsinki principles.

From a pool of 1052 eligible cases, 581 were randomly selected by primary care provider, 81% (n=472) of whom completed the questionnaire. Of those 472 participants, 422 were able to be matched with a responding control. Control subjects were drawn from respondents to the 2005 Member Health Survey (MHS), a general health survey mailed to a random sample of KPNC adult members. We chose MHS participants because this survey asked questions on self-identified race and history of prior cancer. Of the MHS respondents who reported no history of cancer, potential controls were matched by year of birth ±1 year, sex and race to cases (n=1801). We had a 57% response rate for the 736 controls contacted, achieving matched pairs for 422 cases. Non-responders were more likely to be older and female than responders. Given the significantly increased risk profile of organ transplant patients, case-control pairs in which one member reported a history of an organ transplant were excluded (6 cases). In addition, one case-control pair had discrepant self-reported race on the questionnaire and was excluded, leaving 415 case-control pairs for analysis.

Exposure to Supplements

Patients reported if they had regularly (defined as at least once-a-week) used supplements for 3 or more months over the past 10 years from a select list of 7 supplements, which included multivitamins, vitamins A, C, D, E, polypodium leucotomos extract or grape seed extract (GSE). Information on brand, dose, frequency or duration was not ascertained. We included multivitamin use because some reports suggest that certain nutrients, such as vitamins C and E, have synergistic effects,[19,23] and also as surrogate variable for health-conscious pill-taking behavior. Any subject who checked a box next to the supplement in question was considered exposed.

Covariates

Participants also answered questions on variables known to influence SCC risk including skin type, history of freckling (yes/no), eye color, natural hair color, education, family history of skin cancer, history of severe (painful and/or blistering) sunburns, regular (at least once-a-week) peak-time (between 10 am – 4 pm) sun exposure (yes/no), occupational sun exposure (yes/no), tanning bed use (yes/no), high-risk exposures including ultraviolet (UV) light treatment, burn scar, non-healing ulcers, radiation treatment, arsenic exposure, exposure to industrial chemicals (yes/no), and smoking (current vs. former/never). For respondents who reported regular peak-time sun exposure, we also ascertained the average number of hours per week, which we categorized as low (< 6 hours) or high (≥ 6 hours), as well as use of sunscreen (never/rarely vs. much/most of the time) and sun-protective clothing (never/rarely vs. much/most of the time).

Statistical Analysis

Differences in distributions of categorical covariates between cases and controls were analyzed using Pearson chi-square tests. For the matched case-control analysis, we used conditional logistic regression to estimate unadjusted and adjusted odds ratios and Wald 95% confidence intervals in 4 different models. Model 1 estimated crude, unadjusted odds ratios. Model 2 adjusted for all ascertained SCC risk factors. Model 3 adjusted for all SCC

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risk factors as well as exposure to each individual supplement, the use of some of which were correlated. To ensure that our multivariate analyses were not over-adjusted, we created a final model (model 4) limiting the variables to those that were associated with both exposure (individual supplements) and outcome (SCC risk) at the $p<0.20$ level (parsimonious model). *P* values were two-sided. All statistical analyses were performed using SAS, version 9.1, (SAS Institute Inc., Cary, NC).

RESULTS

The average age of participants at index date was 72.5 years ± 8.6 SD (range: 43-85 years). The majority of participants were male (n=514, 61.9%). Compared to controls, cases were more likely to have red or blond hair, blue or grey eyes, and lighter skin types. Cases were also more likely to report current smoking, a family history of skin cancer, a history of childhood freckles, routine sun exposure and severe sunburns, and exposure to other SCC high risk factors (Table 1).

Table 2 shows the risk of SCC in relation to individual supplement use. There was no statistically significant association of SCC risk with respect to use of vitamin A, C, D, or E in any of the 4 models, although the protective effect for multivitamin use was consistent across all models and was borderline significant in the final parsimonious model (OR: 0.71, CI: 0.51-1.00, p= 0.049).

In unadjusted models, users of grape seed extract had a 69% lower odds of SCC compared to non-users (OR: 0.31, CI: 0.10-0.94, p= 0.039). In Model 2, adjusting for all ascertained SCC risk factors (hair and eye color, skin type, education, smoking, family history of skin cancer and history of freckling, sunburns, sun exposure and tanning bed use), the protective effect was more pronounced (OR: 0.22, CI: 0.06-0.87, p= 0.031). Similarly, adjusting for all SCC risk factors as well as other supplement exposures (Model 3) further strengthened the protective association (OR: 0.19, CI: 0.05-0.73, p= 0.017). In the final parsimonious model, presented in the table, grape seed extract was associated with a persistent protective effect (OR: 0.26, CI: 0.08-0.89, p=0.031). No subjects reported use of polypodium leucotomos extract.

Finally, we stratified SCCs as Bowen's disease/in-situ SCC vs invasive SCCs; those with multiple tumors diagnosed in 2004 with both features and those not specified were excluded. Table 3 shows the risk of SCC divided into subtypes in relation to supplement use. Results for multivitamins and GSE were similar for both SCC subtypes. Use of vitamin C supplements was associated with reduced risk of in-situ disease; the confidence intervals for the other supplements were too wide to draw any conclusions.

DISCUSSION

Results from this case-control study show that grape seed extract use is associated with a reduction in risk of cutaneous SCC. This effect was stronger when SCC risk factors, including sun exposure variables, were included in the model. Multivitamin use showed a borderline protective effect. The other supplements that were studied (vitamins A, C, D, and E) did not reveal any associations with SCC risk in adjusted and unadjusted models. In analyses stratified by SCC histologic subtype (in-situ vs. invasive), vitamin C appeared to have a statistically significant protective effect for in-situ SCCs only. This may suggest that vitamin C may have a protective effect that is most pronounced during the early stages of carcinogenesis, or alternatively, may reflect a spurious association due to the multiple comparisons performed. Our stratified analyses were likely underpowered, as evidenced by the substantial widening in confidence intervals.

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GSE has shown promise as a chemopreventative agent in other organs, such as breast, colon, and prostate,[24-27] and trials are currently underway to evaluate its efficacy in these malignancies.[28] However, no epidemiologic studies, to date, have evaluated oral intake of GSE and its association with cutaneous SCC risk in humans. Nevertheless, caution should be used in recommending GSE as a long-term chemopreventative supplement. Reports of side effects of GSE supplementation have included headache, dry, itchy scalp, hives, nausea and dizziness.[29] More concerning are GSEs reported effects on platelet adhesion[30] which may pose additional risks in patients taking anticoagulants such as warfarin, aspirin, non-steroidal anti-inflammatory drugs, or other anti-platelet agents. Also, interactions between GSE and medicines or other supplements have not been carefully studied, and there is evidence to suggest that GSE may interfere with the cytochrome p450 enzyme system.[31] Although oral administration of GSE was well tolerated in people over 8 weeks of a clinical trial,[32] the long-term side effects have not been adequately ascertained.

Our finding of no statistically significant association of SCC risk with individual vitamin supplements is largely consistent with those reviewed and reported in the literature.[4,33,34] Reviews of published human studies investigating the role of dietary factors in the development of keratinocyte carcinomas have not revealed any consistent association between SCC risk and exposure to vitamins A, C or E.[33,34] Large prospective cohort studies have also revealed no association between SCC risk and intake of vitamins A, C or E.[18,35] Pre-diagnostic serum retinol levels were not associated with subsequent risk of SCC.[36] Similarly, several prospective studies using serum concentration of alpha-tocepherol did not reveal any association with subsequent risk of SCC.[36-38] While one double-blind placebo-controlled trial of oral vitamin A showed a reduction in risk of first new SCC in moderate-risk subjects (HR= 0.74, 95% CI 0.56-0.99, p = 0.04),[20] no beneficial effects of retinol were noted in a similar trial of high risk subjects.[39] Large-scale, randomized trials have not shown any association between beta carotene supplementation and SCC risk.[40-42] Although some studies have suggested that specific combinations of vitamins, such as vitamin C and E have synergistic photoprotective effects,[34,43,44] results of a recent trial of a combination of nutritionally appropriate doses of vitamins C, E, beta-carotene, and the minerals selenium and zinc did not reveal any difference in incidence of non-melanoma skin cancer between supplement users and placebo users.[19]

Strengths of this study include a large sample size (n=830) and thorough measurement of risk factors for SCC. However, no information was ascertained on dose, frequency, duration, or brand of supplement use because supplement use was not the primary exposure of interest and our study was not powered to look at this specific association. Also, although the questionnaire was modeled off of a validated instrument on supplement use and cancer risk [45], the accuracy of the survey instrument was not tested. Further limitations of this study include the possibility of recall bias, selection bias, and limitations of generalizability. Our control population came from respondents to the Member's Health Survey and not from the Kaiser Permanente membership at large and may be prone to selection bias. However, previously published papers have reported that respondents to the MHS are representative of the KPNC population.[46] Recall bias is also a potential problem for the self-reported variables, such as sun exposure history. Differential misclassification would result if the cancer diagnosis served as a stimulus for cases to recall supplement use more or less thoroughly than controls. However, the survey collected data on a variety of exposures and supplement use constituted a very small portion of the questionnaire (only one item among 24 items ascertained in questionnaire). The generalizability of our study may be limited because we only studied KPNC members, although previous studies have shown that the KPNC membership is highly representative of the surrounding region except for the tail ends of the income distribution.[46,47] Although use of grape seed extract was reported by a small number of patients (n=17), nevertheless, a total of 2% of our study population reported

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its use, which may seem high for a non-vitamin, non-mineral supplement. However, previously published papers on supplement use within the KPNC adult population have shown that an estimated 32.7% of adult members used at least one non-vitamin, non-mineral supplement in the preceding 12 months, with use highest among whites greater than age 45, which constitutes the majority of our study sample.[48]

In summary, we found a protective effect of GSE use on cutaneous SCC risk. Future studies need to be performed to replicate these findings, and if confirmed, to ascertain the effects of dose or duration of GSE use on SCC risk. Given the potential toxicity of GSE, including platelet dysfunction, more studies are needed to establish the effect, determine optimal dosing and assess side effect profiles.

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Abbreviations

GSE	grape seed extract
NSAIDs	non-steroidal anti-inflammatory drugs
KPNC	Kaiser Permanente Northern California
MHS	Member Health Survey
SCC	squamous cell carcinoma
UV	ultraviolet

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Capsule Summary

- We conducted a case-control study (n=830) at Kaiser Permanente Northern California to examine the association between supplement use and cutaneous squamous cell carcinoma (SCC) risk.
- Self-reported use of grape seed extract was associated with a decreased SCC risk.
- Multivitamin use was associated with a borderline significant reduction in SCC risk.
- Use of vitamins A, C, D and E was not associated with SCC risk.

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Table 1

Risk Factors for Squamous Cell Carcinomas among Cases and Controls

Covariates	SCC n = 415 n (%)	Controls n = 415 n (%)	p value[1]
Pigmentation Variables			
Hair color (red/blond)[2]	102 (24.6)	67 (16.2)	0.003
Eye color (blue/grey)	191 (46.1)	165 (40.0)	0.073
Skin type[3] 1 2 3 4 Missing	 58 (14.0) 76 (18.3) 244 (58.8) 36 (8.7) 1 (0.2)	 20 (4.8) 40 (9.6) 253 (61.0) 90 (21.7) 12 (2.9)	<0.001
Childhood freckles (yes)	224 (54.5)	111 (27.2)	<0.001
UV Exposure Variables			
Sunburns (> 2 severe sunburns)	263 (63.5)	184 (44.7)	<0.001
Occupational sun exposure[4] (yes)	96 (23.2)	85 (20.6)	0.365
Routine sun exposure[5] (yes)	312 (75.2)	284 (68.6)	0.035
≥ 6 hours/week outdoors during peak hours	173 (41.7)	141 (34.0)	0.02
Regular mid-day sun exposure None 1-5 hours protected 1-5 hours unprotected ≥ 6 hours protected ≥ 6 hours unprotected	 103 (24.8) 86 (20.7) 53 (12.8) 109 (26.3) 64 (15.4)	 132 (31.8) 75 (18.1) 67 (16.1) 72 (17.4) 69 (16.6)	<0.001
Tanning bed use (yes)	49 (11.8)	36 (8.7)	0.137
Other Variables			
Education (≥ 4-year college degree)	158 (38.1)	176(42.5)	0.193
Cigarette smoking (current)	29 (7.0)	16 (3.9)	0.046
Family history of skin cancer[6] No Yes Don't Know	 172 (41.6) 136 (32.9) 106 (25.6)	 315 (75.9) 59 (14.2) 41 (9.9)	<0.001
High-risk exposures[7]	177 (42.7)	150 (36.1)	0.055

[1] Pearson Chi-squared test for proportions

[2] Ascertained as "adult natural hair color (prior to graying, if applicable)"

[3] Reaction of skin after exposure to 1 hour of mid-day sun for the first time in the summer with 1=painful or blistering sunburn with no tan, 2=painful sunburn followed by a light tan, 3= mild sunburn followed by a moderate tan, 4= no sunburn followed by a deep tan

[4] At least 2 hours/day of sun-exposure between 10am-4 pm for primary occupation

[5] At least 2 hours/day once-a-week of sun-exposure between 10am-4 pm in the past 10 years

[6] Including natural parents, brothers, and sisters only

[7] UV light treatment, burn scar, non-healing ulcers, radiation treatment, arsenic exposure, exposure to industrial chemicals (yes/no)

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Table 2

Supplement Use among Cases and Controls[1,2]

Supplement	SCC n = 415	Controls n = 415	Crude OR[3] (95% CI)	Adjusted OR[4] (95% CI)
Multivitamins Yes No	 263 (63.4%) 152 (36.6%)	 276 (66.5%) 139 (33.5%)	 0.87 (0.65-1.16)	 0.71 (0.51, 1.00)
Vitamin A Yes No	 31 (7.5%) 384 (92.5%)	 25 (6.0%) 390 (94.0%)	 1.26 (0.73-2.18)	 1.70 (0.82, 3.50)
Vitamin C Yes No	 130 (31.3%) 285 (68.7%)	 149 (35.9%) 266 (64.1%)	 0.82 (0.62-1.09)	 0.80 (0.58, 1.10)
Vitamin D Yes No	 47 (11.3%) 368 (88.7%)	 55 (13.3%) 360 (86.7%)	 0.83 (0.55-1.27)	 0.78 (0.46, 1.32)
Vitamin E Yes No	 130 (31.3%) 285 (68.7%)	 125 (30.1%) 290 (69.9%)	 1.06 (0.79-1.42)	 1.29 (0.84, 1.97)
Grape seed Extract Yes No	 4 (1%) 411 (99%)	 13 (3.1%) 402 (96.9%)	 0.31 (0.10-0.94)	 0.26 (0.08, 0.89)

For Multivitamin: sunburns, regular mid-day sun exposure, cigarette smoking, and vitamin C use

For Vitamin A: childhood freckles, tanning bed use, education, cigarette smoking, vitamin C and grape seed extract use

For Vitamin C: eye color, tanning bed use, education, and grape seed extract use

For Vitamin D: eye color, cigarette smoking, vitamin C and grape seed extract use

For Vitamin E: hair color, eye color, tanning bed use, family history of skin cancer, high risk exposures, vitamin C and grape seed extract use

For grape seed extract: hair color, sunburns, vitamin C use

[1] Use of at least 3 months 307 in the past 10 years

[2] No study participants reported use of polypodium leucotomos extract

[3] Unadjusted (matched on age, gender and race)

[4] Matched on age, gender and race and adjusted for variables associated with exposure (to individual supplements) and outcome (SCC risk) at the $p<0.20$ level. All parsimonious models adjusted for skin type

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Table 3

SCC Risk Among Supplement Users Stratified by Histologic Subtype[1,2,3]

Supplement	OR (95% CI)	
	In-situ n=117	Invasive n=235
Multivitamin	0.76 (0.39, 1.47)	0.72 (0.46, 1.13)
Vit A	0.85 (0.23, 3.22)	2.63 (0.93, 7.50)
Vit C	0.52 (0.27, 0.99)	0.96 (0.62, 1.49)
Vit D	0.35 (0.11, 1.06)	1.20 (0.59, 2.44)
Vit E	1.17 (0.49, 2.83)	1.07 (0.61, 1.87)
Grapeseed Extract	0.19 (0.01, 2.51)	0.27 (0.06, 1.20)

For Multivitamin: sunburns, regular mid-day sun exposure, cigarette smoking, and vitamin C use

For Vitamin A: childhood freckles, tanning bed use, education, cigarette smoking, vitamin C and grape seed extract use

For Vitamin C: eye color, tanning bed use, education, and grape seed extract use

For Vitamin D: eye color, cigarette smoking, vitamin C and grape seed extract use

For Vitamin E: hair color, eye color, tanning bed use, family history of skin cancer, high risk exposures, vitamin C and grape seed extract use

For grape seed extract: hair color, sunburns, vitamin C use

[1] Use of at least 3 months 327 in the past 10 years

[2] n=53 cases not included in table because SCC type either unknown (n=34) or multiple tumors with both subtypes represented in same patient (n=29)

[3] Models adjusted for variables associated with exposure (to individual supplements) and outcome (SCC risk) at the $p<0.20$ level. All parsimonious models adjusted for skin type.