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Dose Response of Retinol and Isotretinoin in the Prevention of Non-Melanoma Skin Cancer Recurrence

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Abstract

Using data from a randomized, double blind, study of the efficacy of retinol or isotretinoin versus placebo on recurrence of non-melanoma skin cancer in high risk subjects, a reanalysis of the original intent to treat analysis was performed in a dose response format. Cox proportional hazards models describe the relationship between dose quartiles of isotretinoin and retinol use and time to first occurrence of squamous cell carcinoma (SCC) or basal cell carcinoma (BCC) in crude and adjusted models. Neither the isotretinoin nor retinol models showed any significance at any quartile for reduction in first BCC or SCC occurrence. Crude and adjusted retinol models show a statistically significant increase in risk of developing an SCC in the first quartile, while only the crude model shows a statistically significant increase in risk in the first quartile of the isotretinoin model. For retinol and SCC hazard ratios for the first quartile were as follows; HR= 2.92, 95% CI 1.67–5.10 crude, HR= 1.95, 95% CI 1.00–3.80 adjusted. For isotretinoin and SCC hazard ratios for the first quartile were as follows; HR=2.38, 95% CI 1.35–4.19 crude, HR= 1.69, 95% CI 0.87–3.31 adjusted. Test for trend was not significant in any of the models. These analyses confirm the results of the original intent to treat analyses and raise an interesting question related to the potential for increased risk for patients in the first quartile of retinol dose.

Introduction

Fifty percent of Americans who live to be age 65 will have skin cancer at least once, making it the most common form of cancer in the United States^{1,2}. Life time exposure to the sun's ultraviolet rays is the most important environmental factor involved in the development of skin cancer, with susceptibility to sunburn likely the most important genetic factor³. Non-melanoma skin cancer (NMSC), which includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is an important target for chemoprevention and ongoing research because of its high incidence. Along with lung, bladder, and breast cancer, skin cancer has

been successfully treated with retinoids including vitamin A and various synthetic derivatives⁴.

The retinoids exert a variety of effects and are vital for embryogenesis, reproduction, vision, glycoprotein production, regulation of inflammation, growth, and differentiation of normal and neoplastic cells in vertebrates, and tend to accumulate preferentially in the skin⁵⁻⁹. The potential chemopreventative properties of retinoids have been studied extensively in various animal models. Epidemiologic studies and clinical trials have demonstrated the activity of vitamin A compounds in the treatment or prevention of skin malignancies¹⁰⁻¹⁹. Actinic keratoses were the first skin lesions to be successfully treated with topically-applied all-trans-retinoic acid^{5;20}.

The SKICAP-BCC/SCC study, a large Phase III study conducted between 1985 and 1990, examined the effect of retinol and isotretinoin on the recurrence of non-melanoma skin cancer among participants with a verified skin cancer history²¹. Based on an intent to treat analysis, the study found no difference between those who received the placebo compared to those who received the isotretinoin or retinol in the time to first new occurrence of BCC or SCC²¹. Over 95% of the study participants reported taking at least half of the total number of capsules and over 80% reported taking at least 75%²¹. However, capsule count adherence was lower for the retinoid groups as compared to the placebo group; 76% and 82%, respectively took at least 3 quarters of their capsules²². Participants in the retinol groups experienced a 1% higher rate of clinical adverse symptoms, mostly elevations in serum cholesterol or liver enzymes, as compared to the placebo group²². This higher rate of adverse symptoms lead to 35% of those in the retinol groups discontinuing use of their study medication prior to completion of the study; by the end of 3 years, only 50% of the randomized participants were still in follow-up^{21;22}.

This current project examines a dose-response approach to determine if the total dose of retinol or isotretinoin affected incidence of new SCC or BCC among this population at high risk for new skin cancers. Because attrition rates in the original study were stated to be high, especially in the retinoid groups and because the SKICAP-SCC/BCC study investigators believe that “due to the less than anticipated duration of participation for participants in the trial the effect of retinoids in higher risk subjects was not truly evaluable” this dose response analysis is being done to understand if there was a reduction in BCC/SCC recurrence in participants who were able to stay on study and complete the intervention²².

Methods

A full description of the study design and methods of the SKICAP-BCC/SCC study have been previously published^{21;22}. Eligible participants were those who had: (1) at least four biopsy-proven skin cancers, (2) one NMSC within 12 months of consent, (3) no diagnosis of melanoma or internal cancer within the past year, (4) were between 21 and 85 years of age, if female, not of childbearing potential, and (5) willing to attend visits at the study clinic, visiting the study dermatologist or personal dermatologist yearly for at least the next three years.

Between January 1985 and June 1990, 719 people in the Tucson, Phoenix and Yuma, Arizona areas and the San Diego, California area consented to the study. Five hundred twenty-five were found to be eligible for randomization and successfully completed a run-in period by achieving a 75% adherence level to the daily capsule intake regimen²¹. Participants were randomly assigned to receive either 25,000 IU of oral retinol (n=173), isotretinoin (5mg for those under 145lbs and 10mg for those equal to or greater than 145lbs) (n=178) or placebo (n=174), daily for three years²¹.

Estimation of Total Dose Received

For the current dose response analysis, the total number of pills taken by each participant enrolled in the treatment arms was calculated based on physical pill count adherence percentages maintained in the electronic data base. Compliance greater than 100% was set to equal 100%. The total number of pills consumed was then converted to total dose per kilogram for each participant. Supplemental Vitamin A intake information (yes or no) was collected at baseline and monitored throughout the study. Very few study participants reported any supplemental Vitamin A intake (9.3%) at baseline (supplemental intake greater than 5000 IU daily was an exclusionary criteria) and a comparison of supplemental vitamin A intake at baseline among the three treatment groups revealed no statistical difference (p=0.49). Therefore no attempt was made to add supplemental Vitamin A use into total dose per kilogram.

Assessment of End Points

All skin cancer end points were monitored after randomization and confirmed by pathology. Participants were examined for skin lesions by a study dermatologist or their own dermatologist at least once a year, and underwent a full-body skin examination by a study dermatologist at study end. Participants with suspicious skin lesions were referred for biopsy and treatment, and were closely followed by study staff to ensure that biopsies were performed and a diagnosis obtained. In addition, endpoints were identified by participant self-report at study follow-up visits, by review of pathology records of dermatologists, pathology laboratories and the Southeast Arizona skin cancer registry. Diagnostic pathology slides were obtained on all biopsies, centrally reviewed and confirmed by the study dermatopathologist. Participants were encouraged to continue the study regimen even if a new BCC or SCC was diagnosed.

This analysis mimics the original intent to treat analysis using a dose response approach. Quartiles of total intervention use were generated for the retinol and isotretinoin group. Two primary differences are inherent in the current dose response approach analysis. The original intent to treat analysis adjusted for *apriori* selected variables including self-reported large mole and freckle count (described as those moles greater in circumference than a pencil eraser). Along with missing counts for a significant proportion of the study population, the mole and freckle count in itself does not appear to contribute substantially more than information already included between the skin reaction to sun and typical hours of sun exposure. Secondly, lesions diagnosed as in-situ were not included in the number of NMSC contributing to the skin cancer history in the original analysis; the current dose response approach includes SCC-in situ, Bowen's and keratoacanthomas as contributing to both the

NMSC history and new cutaneous cancer occurrences because it was felt there is truly no clinically significant difference between these types of in-situ lesion and what was diagnosed as SCC or BCC”.

Other Variables

In initial analyses multiple baseline variables commonly associated with risk for NMSC were included as potential confounders. Total reported usual weekly sun exposure was a combination of self-reported total weekday hours and weekend hours of sun exposure dichotomized to 0–10 hours or greater than 10 hours. This delimitation of exposure was selected to maintain consistency with the breakdown of exposure in the original analysis. The variables skin reaction to the sun, eye color, hair color, mother’s ethnic origin and father’s ethnic origin were categorized according to known phenotypic traits that would place an individual at higher or lower risk of NMSC. The variable skin reaction to the sun was split into four categories: always/usually burn (tan little/usually burn-tan minimally), burn moderately (tan average), burn minimally (tan easily and above average and rarely/never burn (tan easily). The variable smoking status was split into three categories, never smoker, former smoker, and current smoker). History of NMSC was considered separately for both BCC and SCC and dichotomized into those with a history of less than 10 or a history of greater than or equal to 10 prior BCC or SCC. In addition months on study was assessed as both an effect modifier and a confounder because total dose taken is inextricably tied to how long a participant was active in the study.

Analysis

All analyses were performed using intercooled STATA version 9.0 (ref-StataCorp, 4905 Lakeway Drive, College Station, Texas). Chi square tests compared basic demographic characteristics between the quartiles of use for each of the interventions and one way analysis of variance was used to compare means. T-tests were used to compare both the mean dose of retinol and isotretinoin in the first quartile to the placebo group. A Kruskal-Wallis test was used to compare median time on study for those taking retinol by quartiles.

To examine the relationships between quartiles of total retinol dose received versus placebo and total isotretinoin dose received versus placebo on the development of NMSC, hazard ratios and 95% confidence intervals were estimated. Cox proportional hazards models estimated time to the development of new BCC or SCC occurrence. Participants who developed both a new BCC and SCC occurrence during the study period were included in both the BCC and the SCC analysis. Test for trend was accomplished by estimating Cox proportional hazards models without using the categorical dose variable. Potential confounding factors were evaluated in initial models by comparing the adjusted and unadjusted hazard ratios. Factors were included in the final models only if the adjusted hazards ratio changed by greater than 10%. Months on study was evaluated as a potential effect modifier by creating an interaction term including months on study and dose. Likelihood ratio tests were used to assess the significance of this interaction term.

The examination included three modeling approaches: a crude model, a model adjusted for age, gender and months on study, and a model adjusted for age, gender, skin reaction to the

sun, total time in sun, months on study and history of NMSC. In addition, three alternative modeling approaches were performed in an attempt to understand the increased risk associated with the first dose quartile of retinol and SCC. These models were as follows: 1) A model was constructed where all subjects who had not been on study at least six months were removed from the data set; 2) All events that occurred in the first six months were removed from the data set but all subjects were kept; and 3) Retinol dose was converted to mg (1µg retinol=3.33 IU vitamin A activity) and retinol and isotretinoin dose were added together, calculated into mg/kg and analyzed as one treatment group.

Results

Of the 525 participants in the study, 102 participants had no diagnosis of either a new BCC or SCC after randomization. Two-hundred had at least one new SCC diagnosed after randomization, and 132 had at least one new diagnosis of BCC after randomization. One-hundred-seventy participants were diagnosed with both a new BCC and SCC after randomization. Median time on study was 30.4 months for all participants (30.4 months for those on retinol, 29.7 months for those on isotretinoin and 31.3 for those on placebo).

The baseline characteristics did not differ by retinol dose quartiles with the exception of age (Table 1). Those in the highest quartile of dose were younger with a mean age of 61 years ($p=0.0009$) as compared to participants in the other dose quartiles (68, 69 or 67 years) or placebo (65 years). Table 2, which indicates the distribution of baseline characteristics for participants by quartiles of isotretinoin dose, reveals no differences between the dose groups with the exception of gender ($p=0.011$). The two groups with the highest intake of isotretinoin were 80% and 84% male, while the two lowest intake groups were 53% and 66% male compared to the placebo group that was 72% male.

Table 3 examines the relationship between retinol dose level, including placebo group participants and time to first new occurrence of BCC or SCC. For SCC, the crude and partially adjusted models show a statistically significant increase in risk of developing a new SCC for the first dose quartile with the fully adjusted model just meeting statistical significance at the $p=0.05$ level. Test for trend was not significant. In the crude model those in the first quartile of retinol dose have a HR of 2.92 (95% CI 1.57–5.10) and this increased HR also remains in the adjusted models, 2.06 (95% CI 1.06–4.80) and 1.95 (95% CI 1.00–3.80) respectively. None of the three models showed any significance at any level for new BCC occurrence.

The relationships between the synthetic retinoid isotretinoin dose level and new occurrence of BCC or SCC (Table 4) revealed a different outcome. Only the crude model for SCC showed a statistically significant increased HR in the first dose quartile, 2.38 (95% CI 1.35–4.19). For both the partially and fully adjusted model, there was no statistically significant increase in risk for participants in the first dose quartile, 1.17 (95% CI .724–1.88) and 1.69 (95% CI .866–3.31), respectively. Test for trend was not significant in any of the models. Again there were no significant results for new BCC occurrence.

In an attempt to identify potential alternate explanations for the increased risk of SCC in the first retinol quartile, additional comparisons were made. The mean dose of retinol in the first quartile (48,481.1 mg/kg) indicated that the participants received a dose statistically significantly greater than those in the placebo group ($p<0.0001$). Not unexpectedly, median time on study was less than for those in the first quartile as compared to the other three quartiles. The median time on study for those taking retinol in quartile one was 6.6 months, quartile two was 25.1 months, quartile three was 38.8 months and quartile four was 53.4 months ($p=0.0001$). In addition, alternate analysis approaches involving the removal of all participants not on study for at least six months, removal of all NMSC diagnosis occurring in the first six months and conversion of the intervention doses in order to create a total dose and one intervention group did not significantly change the models.

Off study reasons were investigated by quartile of dose received. For both retinol and isotretinoin the major reason participants left the study in the lowest quartile were for toxicity consistent with the interventions (retinol=46.5%, isotretinoin=52.0%) and unwillingness to continue (retinol=30.3%, isotretinoin=31.9%). For quartile two the majority of subjects completed the study (retinol=62.8%, isotretinoin=53.3%) and a smaller percentage were unwilling to continue (retinol=18.6%, isotretinoin=24.4%). For quartiles three and four the majority completed the study, with fewer numbers unwilling to continue.

Discussion

These analyses evaluating dose response confirm the findings of the original intent to treat analysis. The daily regimen of 25,000 IU of retinol or 5 or 10 mg of isotretinoin were not effective at preventing new occurrences of SCC or BCC among a population with histories of multiple cutaneous cancers. In the current analysis all models, crude and adjusted, evaluating SCC occurrence and actual retinol dose level received showed that there was a statistically significant increase in risk of recurrence for those in the first dose quartile, even after adjustment for potential confounders such as age, gender, skin reaction to sun, total time in sun, months on study and history of NMSC. Test for trend was not significant either for protection or for increased risk.

In the SKICAP-BCC/SCC study no protective effect for development of new SCC or BCC was found for either isotretinoin or retinol using the intent to treat analyses. The original study reported fairly good compliance for those who remained on study but also indicated that the attrition rates were high in all groups. During conduct of the SKICAP-BCC/SCC study, new toxicity information about one of the intervention agents surfaced²¹. This information was conveyed to all participants because of the double blinded nature of the trial design. This strong message of potential side effects given to each individual participant by the study interviewers may have increased the attrition rate over what would have been expected. The study population became sensitized to slight deviations from their normal health and could have ascribed it to their study medication and stopped the study. This increased attrition diminished the ability of the trial to detect a difference between the placebo and treatment groups and thus, the trial was not considered fully evaluable²².

An additional limitation in longer studies such as SKICAP, is in separating the effects of normal aging and increased prevalence of chronic disease with potential adverse effects consistent with intervention. Recruiting a population with histories of multiple cutaneous cancers resulted in the mean age of the study group being slightly above the typical retirement age of 65 years. Substantial changes in lifestyle and perceived health can accompany the changes associated with this stage regardless of participation in intervention trials.

The current standard for analysis of clinical trial data is intent to treat analysis (also known as use-effectiveness). Intent to treat analysis seeks to answer the question “Is it better to adopt a policy of treatment A if possible, with deviations if necessary, or a policy of treatment B if possible, with deviations if necessary, for patients with a particular medical condition?”^{23;24}. The intent to treat analysis requires inclusion of all randomized patients in the analysis, in their originally randomized assignment groups, regardless of whether they remained on protocol for the duration of the study²⁵.

Arguments for use of intent to treat are many. Intent to treat analysis, in the presence of non compliance, reduces differences among treatments making it more difficult to demonstrate that one is better than the other, retains the original sample size and power, controls for bias, prevents a researcher from obscuring the facts in favor of their own theories, and maintains a very conservative analysis^{24;26}. Because the randomization process helps control for potential confounders, measured and unknown, it is believed that only the original assignment retains this guarantee^{23;24;27}. If participants who deviate from the protocol because of toxicity, age, disease severity, etc. are omitted, then groups may not be comparable and the biases that were originally controlled for through randomization may affect the outcome of the analyses. In addition, the argument has been made that it is not reasonable to generalize study results to only compliant participants with similar disorders, because the majority of people are noncompliant under normal circumstances and do not adhere to a proscribed regimen^{24;27}.

There are also arguments against the exclusive use of intent to treat analysis for clinical trial data. Sheiner et al. argue that intent to treat analyses do not provide valid significance levels, estimates, or interval estimates either for use-effectiveness in regular medical practice or for the effect of the actually administered therapy (method effectiveness)²³. These researchers argue that method-effectiveness maybe be more relevant to medical decision making than use-effectiveness and that trials should be designed and analyzed to provide both results. Understanding potential benefit given full compliance and the expected benefit averaged over rates of compliance in a particular trial are considered to provide important information, especially for clinicians²³. The intent to treat estimate only provides an average prognosis of a mixture of compliers and of people who may not have taken the drug at all or who left the study prematurely. This average prognosis may not apply to any individual participant. Substantial deviations from the protocol through either loss to follow-up or drop out can dilute the data and diminish the ability of a trial to detect a difference between effects of treatment^{23;27}.

Intent to treat analysis reveals the answer to the question “Is a treatment effective?” while an explanatory analysis seeks to answer the efficacy question “Can this treatment work?”. The secondary analysis of these data using a dose response approach seeks to answer the question “Can this treatment work?” because it examines the study from a compliance point of view, and takes into consideration the total dose of intervention consumed by each individual participant.

Overall reported toxicity of level two or greater in the SKICAP BCC/SCC study was mild, and the isotretinoin-treated group reported more side effects than either the placebo or retinol group. The majority of toxicities reported were in the mucocutaneous category²¹. However, by year 2 (28 months) of the study (visit 5), only 63% of the original 175 subjects remained on study in the isotretinoin treatment group, 68% of the 173 remained on study in the retinol group, and 72% of the 173 in the placebo group remained on study.

One of the major drawbacks of the retinoids is the toxicity associated with the physiologic accumulation of excessive amounts. The first and classical reported cases of acute hypervitaminosis A involve Eskimos and Arctic explorers ingesting polar bear or seal liver meat, and then developing severe headaches, drowsiness, irritability, nausea, and vomiting, erythema and desquamation of the face, trunk, palms and soles of the feet with symptoms resolving in 7 to 10 days²¹. Absorption differences and variability in the risk of accumulation and toxic effects can differ depending on the retinoid being used. Synthetic forms such as isotretinoin are thought to distribute more uniformly in the body and are thought to be less likely to cause the severe adverse effects related to the accumulation of excessive levels of retinol in the liver. Unfortunately, the various synthetic retinoids are associated with additional adverse effects, rather than providing the answer to eliminate toxicity related to high retinoid intake. Side effects of the synthetic retinoids include mucocutaneous drying and chapping leading to cheilitis, facial dermatitis, conjunctivitis, dryness of the nasal mucosa with minor nosebleeds, dry mouth with thirst, xerosis, hair loss, palmoplantar desquamation, stratum corneum fragility or easy peeling due to minor frictional trauma and scratching, paronychia and nail abnormalities²⁸.

Our dose response analysis evaluated participants by original group assignment but based on total dose per kilogram body weight; therefore, the characteristics of the groups based on the original randomization remain intact. Additionally we looked at the characteristics of subjects in each treatment group by dose quartile, and there were few differences by quartile. Those in the highest quartile of retinol appeared to be younger, possibly indicating that those participants who were younger were able to stay on study longer or more able to tolerate the intervention. However, many of the potential adverse effects of the retinoid dosing such as skin and mucous membrane dryness and hair loss are also common occurrences with aging. In the retinoid intervention study with its older age population it was not possible to discern some of the potential intervention related adverse effects from age related changes. For isotretinoin there were differences in quartile by gender indicating that men may have stayed on study longer.

Models with potential confounders such as skin reaction to the sun, total time in the sun, months on study, history of NMSC, age and gender were assessed in our dose response

analyses. Based on the fully adjusted models these analyses indicate that there may be an increase in risk of new SCC occurrence for those in the lowest quartile of retinol. In addition three alternative analyses were done in an attempt to better assess the increased risk in the first quartile for retinol and SCC. Unfortunately, none of the three alternative analyses of the data set provided an outcome significantly different from the original dose response analysis.

In order to try and explain why participants in the lowest quartile of total retinol were at increased risk for developing a new SCC, we compared time on study, mean dose, and off study reasons, by quartile of dose. Those in the lower quartile of dose were on study for less time than those in the upper quartiles, however this is to be expected as the total amount of intervention a participant took would be heavily dependent on the amount of time they were on study. In addition, mean dose between the placebo group and the first quartile was significantly different so participants in the first quartile did receive drug. The reasons why participants in the first quartile went off study were quite different from those in the other quartiles. First quartile participants most frequently reported their reason for going off study as toxicity consistent with the intervention, and in the other three quartiles participants went off because they were exiting or unwilling to continue (small percentage). Median time on study for those with and without a new BCC or SCC occurrence during the study was compared by quartile of dose and showed no evidence that those who developed a new NMSC had a shorter time on study versus those who did not.

The present project examined the efficacy of retinoid interventions in preventing the development of new NMSC among a population with a history of multiple and recent cutaneous cancers. Side effects were more prevalent and greater attrition was associated with the isotretinoin. A review of 13 serum retinol studies, both prospective and retrospective, and a large case control study showed that low vitamin A levels existed in the cancer populations and potentially played a role for incidence, basically suggesting that the lower the serum vitamin A level, the greater the cancer risk^{29,30}. However other studies have suggested that low serum retinol may be a metabolic consequence of cancer rather than a precursor of cancer³¹.

Dietary intake studies of the association between retinol have shown inconsistent results with BCC and SCC³². Of the 11 dietary studies reviewed only one hospital based case control study by Wei et al. showed an inverse association between the use of vitamin A supplements in the last 5 years and the development of BCC (OR=0.20, 95% CI, 0.06–0.62)¹⁸.

Oral retinoid therapy seems to prevent or delay development of cutaneous carcinomas for patients with some cutaneous diseases with a high risk of malignancy, such as xeroderma pigmentosum, Mibelli's porokeratosis, Gorlin's disease, Ferguson-Smith disease and solar keratosis³³. In addition, several small studies that treated patients with other cutaneous diseases who also already had BCC with high dose retinoids, oral or topical, reported that the tumors responded well to the treatment and, in many cases, the treatment reduced the number of existing tumors or prevented onset of new tumors^{13;15;17;34–37}. Thus there is substantial literature indicating that retinoids may have the ability to prevent BCC.

A nested cohort study compared patients' own tumor experience while using and not using retinoids for patients participating in a Psoralen + UVA treatment (PUVA) follow-up study who reported at least 1 year of substantial retinoid use between 1985 and 2000. They found that retinoid use was associated with a 30% reduction in SCC ($p=0.02$)¹⁹. The incidence of SCC significantly decreased during years of substantial retinoid use (Incidence rate ratio=0.79, 95% CI 0.65–0.95), but there was no association between BCC incidence and oral retinoid use¹⁹. In a study of 981 subjects who had two or more previously confirmed BCCs randomized to 10 mg isotretinoin or placebo, there was no significant difference in the cumulative percentage of patients with an occurrence of BCC at a new site or the annual rate of BCC formation after 36 months. Subjects reported significant adverse systemic effects¹¹. The combined results of these two studies indicate no effect of retinoids on BCC development but significant reduction on cutaneous SCC development associated with retinoid intervention. In addition, studies done with the retinoid acitretin and etretinate in renal transplant recipients have shown that these agents are effective in reducing NMSC and AK incidence in this high risk population^{38–41}.

There has been little recent research on retinoids and skin cancer prevention. Recent studies of head and neck squamous cell cancer (HNSCC) have been null. In a randomized, 8 year trial (3 years on intervention and 4 years of follow-up) in 1,190 patients with a history of stage I or II HNSCC, low dose isotretinoin was found to be no more effective in reducing the rate of second primary tumors than placebo (HR=1.06, 95% CI 0.83–1.35) or increasing the rate of survival (HR=1.03, 95% CI 0.81–1.32)⁴². In addition Bonelli et al. found no advantage for patients previously treated for Stage II and IV HNSCC who took isotretinoin as compared to those in the control group, 5 year actuarial survival 58.9% for those in treatment versus 57.2% in the control group ($p=0.94$)⁴³.

These analyses confirm the results of the original intent to treat analyses and in addition raise an interesting question related to patients in the first quartile of dose for retinol and increased risk. Multiple attempts were made to understand if this increase in risk could be explained by different characteristics of the study population to no avail. History provides that other vitamin compounds including retinoids have been investigated by chemoprevention studies and were found to increase the risk for cancer rather than protect from cancer. Of note is a lung cancer prevention study, the CARET study, which found an increased risk for lung cancer and death (28% and 17%, respectively) when a high risk population of 18,314 participants (history of smoking and asbestos exposure) were randomized to daily beta-carotene (30 mg) and retinyl palmitate (25,000 IU)⁴⁴. The increase in risk found for NMSC when retinoids are used alone rather than in combination with other compounds remains to be further investigated.

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Table 1

Baseline characteristics by quartiles of dose for retinol (n=347)

Variable	Quartiles of Total Dose					p-value
	Placebo (0)	1347.7 mg/kg	1347.7–2580.5 mg/kg	2580.6–3994.6 mg/kg	>3994.6 mg/kg	
Age (years)	64.8 ± 10.5	67.7 ± 8.0	68.7 ± 7.06	67.1 ± 8.86	60.9 ± 10.38	0.0009
Male gender	126 (72.4)	32 (72.4)	33 (76.7)	34 (77.3)	28 (65.1)	0.710
Skin reaction to sun						0.607
Always or usually burn tan little or minimal	70 (40.2)	20 (46.5)	16 (37.2)	20 (45.5)	14 (32.6)	
Burn moderately/tan average	68 (39.1)	18 (41.9)	15 (34.9)	16 (36.4)	16 (37.2)	
Burn minimally/tan easily	15 (8.6)	1 (2.3)	6 (14.0)	1 (2.3)	6 (14.0)	
Rarely/never burn tan easily	21 (12.1)	4 (9.3)	6 (14.0)	7 (15.9)	7 (16.3)	
Total hours in sun	14.4 ± 12.4	15.3 ± 11.6	16.1 ± 11.7	12.6 ± 9.7	13.4 ± 11.1	0.646
History of NMSC						
SCC						0.471
<10	155 (89.1)	39 (90.7)	42 (97.7)	39 (88.6)	40 (93.0)	
10	19 (10.9)	4 (9.3)	1 (2.3)	5 (11.4)	3 (7.0)	
BCC						0.271
<10	82 (47.1)	23 (53.5)	25 (58.1)	18 (40.9)	16 (37.2)	
10	92 (52.9)	20 (46.5)	18 (41.9)	26 (59.1)	27 (62.8)	

Abbreviations are as follows: NMSC, nonmelanoma skin cancer; SCC, squamous cell carcinoma; BCC, basal cell carcinoma

Table 2

Baseline characteristics by quartiles of dose for isotretinoin (n=352)

Variable	Quartiles of Total Dose					
	Placebo (0)	56.36 mg/kg	56.36–124.0 mg/kg	125.0–223.9 mg/kg	>223.9 mg/kg	p-value
Age (years)	64.8 ± 10.5	67.9 ± 7.7	64.6 ± 9.9	66.4 ± 10.1	61.5 ± 11.3	0.438
Male gender	126 (72.4)	29 (65.9)	24 (53.3)	36 (80.0)	37 (84.1)	0.011
Skin reaction to sun						0.737
Always or usually burn tan little or minimal	70 (40.2)	16 (36.4)	20 (44.4)	18 (40.0)	20 (45.5)	
Burn moderately/tan average	68 (39.1)	18 (40.9)	18 (40.0)	21 (46.7)	15 (34.1)	
Burn minimally/tan easily	15 (8.6)	3 (6.8)	3 (6.7)	3 (6.7)	7 (15.9)	
Rarely/never burn tan easily	21 (12.1)	7 (15.9)	4 (8.9)	3 (6.7)	2 (4.6)	
Total hours in sun	14.4 ± 12.4	12.3 ± 9.0	14.0 ± 11.1	11.8 ± 8.7	15.3 ± 15.7	0.544
History of NMSC						
SCC						0.498
<10	155 (89.1)	40 (90.9)	40 (88.9)	44 (97.8)	40 (90.9)	
10	19 (10.9)	4 (9.1)	5 (11.1)	1 (2.2)	4 (9.1)	
BCC						0.300
<10	82 (47.1)	22 (50.0)	24 (53.3)	29 (64.4)	20 (45.5)	
10	92 (52.9)	22 (50.0)	21 (46.7)	16 (35.6)	24 (46.6)	

Abbreviations are as follows: NMSC, Nonmelanoma skin cancer; SCC, squamous cell carcinoma; BCC, basal cell carcinoma.

Table 3Relationship of retinol dose level to first recurrence of BCC or SCC^a

Model	BCC			SCC		
	HR	p-value	95%CI	HR	P-value	95%CI
Crude						
Units/Kg dose						
0 (placebo)	-			-		
1347.7	1.38	0.137	.903–2.09	2.92	<0.000	1.67–5.10
1347.7–2580.5	0.996	0.985	.665–1.49	1.26	0.454	.684–2.33
2580.6–3994.6	1.31	0.144	.912–1.88	1.53	0.090	.940–2.48
>3994.6	0.931	0.710	.639–1.36	0.724	0.260	.414–1.27
Test for trend		p=0.793			p=0.783	
Adjusted (1)^b						
Units/Kg dose						
0 (placebo)	-					
1347.7	1.17	0.528	.724–1.88	2.06	0.033	1.06–4.00
1347.7–2580.5	0.916	0.677	.605–1.39	1.03	0.935	.548–1.92
2580.6–3994.6	1.21	0.303	.839–1.76	1.30	0.301	.792–2.13
>3994.6	1.06	0.777	.706–1.59	0.934	0.820	.517–1.69
Test for trend		p=0.547			p=0.650	
Adjusted (2)^c						
Units/Kg dose						
0 (placebo)	-					
1347.7	1.18	0.501	.728–1.92	1.95	0.049	1.00–3.80
1347.7–2580.5	1.00	0.987	.659–1.53	1.29	0.436	.681–2.43
2580.6–3994.6	1.33	0.141	.910–1.94	1.27	0.350	.769–2.10
>3994.6	0.853	0.466	.557–1.31	1.03	0.925	.562–1.88
Test for trend		p=0.853			p=0.419	

^a Abbreviations are as follows: BCC, basal cell carcinoma; SCC, squamous cell carcinoma; CI, confidence interval; HR, hazard ratio; NMISC, nonmelanoma skin cancer

^b Adjusted for age, gender and months on study

^c Adjusted for age, gender, skin reaction to sun, total time in sun, months on study and history of NMSC

Table 4Relationship of isotretinoin dose level to first recurrence of BCC or SCC^a

Modal	BCC			SCC		
	HR	p-value	95%CI	HR	P-value	95%CI
Crude						
Mg/Kg dose						
0 (placebo)	-			-		
56.36	1.49	0.032	1.03-2.16	2.38	0.003	1.35-4.19
56.36-124.0	1.02	0.907	.697-1.50	1.33	0.31	.762-2.33
125.0-223.9	0.884	0.556	.586-1.33	1.39	0.02	.840-2.29
>223.9	1.01	0.956	.704-1.45	0.998	0.10	.584-1.68
Test for trend		p=0.697			p=0.631	
Adjusted (1)^b						
Mg/Kg dose						
0 (placebo)	-					
56.36	1.41	0.119	.916-2.17	1.68	0.116	.879-3.22
56.36-124.0	1.02	0.907	.692-1.51	1.50	0.170	.840-2.68
125.0-223.9	0.841	0.414	.556-1.27	1.33	0.269	.802-2.20
>223.9	1.03	0.891	.704-1.50	1.08	0.753	.638-1.86
Test for trend p=		p=0.797			p=0.650	
Adjusted (2)^c						
Mg/Kg dose						
0 (placebo)	-					
56.36	1.03	0.889	.653-1.64	1.69	0.123	.866-3.31
56.36-124.0	0.905	0.620	.609-1.34	1.48	0.190	.823-2.64
125.0-223.9	0.841	0.419	.551-1.28	1.53	0.100	.921-2.57
>223.9	1.23	0.297	.836-1.80	1.27	0.385	.738-2.19
Test for trend p=		p=0.789			p=0.108	

^a Abbreviations are as follows: BCC, basal cell carcinoma; SCC, squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; NMISC, nonmelanoma skin cancer

^b Adjusted for age, gender and months on study

^c Adjusted for age, gender, skin reaction to sun, total time in sun, months on study and history of NMSC