Photochemistry and Photobiology, 2008, 84: 284–288

Protection from Sunburn with β-Carotene—A Meta-analysis†

Wolfgang Köpcke[1] and Jean Krutmann*[2]

[1]Department of Medical Informatics and Biomathematics, Münster University Hospital, Münster, Germany
[2]Institut für Umweltmedizinische Forschung (IUF) at the Heinrich-Heine-University Düsseldorf gGmbH, Germany

Received 10 August 2007, accepted 24 October 2007, DOI: 10.1111/j.1751-1097.2007.00253.x

ABSTRACT

Nutritional protection against skin damage from sunlight is increasingly advocated to the general public, but its effectiveness is controversial. In this meta-analysis, we have systematically reviewed the existing literature on human supplementation studies on dietary protection against sunburn by beta-carotene. A review of literature until June 2007 was performed in PubMed, ISI Web of Science and EBM Cochrane library and identified a total of seven studies which evaluated the effectiveness of β-carotene in protection against sunburn. Data were abstracted from these studies by means of a standardized data collection protocol. The subsequent meta-analysis showed that (1) β-carotene supplementation protects against sunburn and (2) the study duration had a significant influence on the effected size. Regression plot analysis revealed that protection required a minimum of 10 weeks of supplementation with a mean increase of the protective effect of 0.5 standard deviations with every additional month of supplementation. Thus, dietary supplementation of humans with β-carotene provides protection against sunburn in a time-dependent manner.

INTRODUCTION

Ultraviolet (UV) radiation exerts a number of detrimental effects on human skin (1,2). The most familiar one, which is virtually known to every human being, is a sunburn reaction, which develops within hours after exposure to shorter wavelengths UVB (290–315 nm) radiation. Avoidance of sun exposure and topical application of sunscreens prior to exposure represent the established strategies for protection against sunburn (3). In recent years, however, nutritional protection against sunburn formation has been discussed as well (4–6). Among the substances that are being suggested for such a nutritional approach β-carotene seems to be an interesting candidate. β-Carotene is a potent biological antioxidant. It is a strong singlet oxygen quencher *in vitro* and experiments in animal models indicate that β-carotene may provide skin photoprotection *in vivo* (7,8). Systemic photoprotection by β-carotene supplementation could contribute significantly to skin health and add to photoprotection by sunscreens, because it could provide a lifelong, overall, basic protection against the development of sunburn reactions (6). In this study, we have therefore conducted a meta-analysis of the existing literature about the effectiveness of β-carotene for sunburn prevention. We have focused on this substance and this biological end point because—to the best of our knowledge—only for β-carotene and only for prevention of sunburn the number of studies that exist is sufficient to allow a meta-analysis.

METHODS

The literature until June 2007 was searched using the following databases: PubMed, ISI Web of Science (Science Citation Index Expanded) and EBM Cochrane library using the keywords "betacarotene" or "carotenoids" and "sunburn." In addition to the mentioned databases, manual search was done of references cited in the selected articles as well as in selected books on nutrition and skin. No language restriction was applied.

Primary inclusion criteria for the selection of relevant articles were original publications about clinical trials. Case reports, reviews and editorials were not considered eligible.

The selected articles were reviewed and data were abstracted by means of a standardized data-collection protocol using the following criteria: Only placebo-controlled clinical studies on the supplementation with β-carotene on protection against sunburn were used.

We identified seven studies, the characteristics of which are listed in Tables 1 and 2, and their full references are cited in the reference list at the end of this report (9–15).

A classical meta-analysis for studies with continuous outcome was performed according to published work (16,17). In studies of the effects of a treatment that measure the outcome on a continuous scale, a natural effect size is the standardized mean difference (SMD). The SMD is the difference between the mean outcome in the treatment group and the mean outcome in the control group divided by the within group standard deviation. Once an effect size is estimated for each study, the next step is to summarize these results in an overall effect. To test whether the sample effect sizes are themselves homogeneous (from a single population), one uses the so-called Q statistics, a form of weighted sums-of-squares, which can be tested against a χ^2 distribution with $n-1$ degrees of freedom. A significant result indicates that the variance is greater than expected due to sampling error. In this case, the assumption of a fixed-effects model that there is a single true effect in all studies (or for each group of studies) and that any observed variation is due to sampling error is not true and an alternate model, the random-effects model, which assumes that there is an average effect with a certain degree of variation around this mean, is used.

†This paper is part of a special issue dedicated to Professor Hasan Mukhtar on the occasion of his 60th birthday.

*Corresponding author email: krutmann@rz.uni-duesseldorf.de (Jean Krutmann)

© 2007 The Authors. Journal Compilation. The American Society of Photobiology 0031-8655/08

Table 1. Study characteristics (sample size, duration, and dose).

Study name	β-Carotene sample size	Control sample size	Duration (weeks)	Daily dose (mg)	Total dose (mg)
Garmyn *et al.* (9)	8	6	3	90	1890
Gollnick *et al.* (10)	8	6	12	30	2520
Heinrich *et al.* (11)	12	12	12	24	2016
Lee *et al.* (12)	11	11	24	60	10 080
Mathews-Roth *et al.* (13)	17	12	10	180	12 600
McArdle *et al.* (14)	8	8	8	15	840
Stahl *et al.* (15)	8	8	12	25	2100

Table 2. Methods and results of erythema assessment.

Study name	Erythema assessment	Effect: size and direction	β-Carotene effect (mean ± SD)	Placebo effect (mean ± SD)
Garmyn *et al.* (9)	Minimal erythema dose	+	1 ± 17.7471	2.9 ± 15.9142
Gollnick *et al.* (10)	Number of body areas with higher or lower erythema grades	+	0.5263 ± 0.7618	0.0526 ± 0.8366
Heinrich *et al.* (11)	Chromametry α-values	−	4.7 ± 2.488	7.5 ± 1.6
Lee *et al.* (12)	Minimal erythema dose	+	25.3 ± 4.925	20.9 ± 4.6904
Mathews-Roth *et al.* (13)	Minimal erythema dose	+	11.4706 ± 3.3435	9.8958 ± 4.7212
McArdle *et al.* (14)	Minimal erythema dose	+	28 ± 2.6667	28 ± 2.6667
Stahl *et al.* (15)	Δa-values	−	7 ± 2.9	10.7 ± 3.3

Additionally one can test whether there is a linear relationship between a continuous moderator variable (*e.g.* dose and duration) and the effect sizes with a so-called meta-analytic regression (18).

The calculations and graphical presentation were produced with the following software: Comprehensive Meta-Analysis, S-Plus and SAS.

RESULTS

The *Q*-test for heterogeneity was statistically significant (Table 3). Thus, a fixed-effects model approach would not be appropriate and therefore, the random-effects model and meta-regression were used for meta-analysis of the seven studies. As is shown in Table 3, assessment of the effect of β-carotene supplementation on the development of a sunburn reaction revealed that there is a significant effect ($P = 0.0089$) in the size of 0.8 standard deviations (95% CI from 0.2 to 1.4) (Fig. 1).

In addition, a meta-regression with the moderator variables daily dose, duration and total dose showed that only the study duration had a significant influence of the effected size ($P = 0.00025$) (Fig. 2). The regression plot with 95% confidence bounds identified 10 weeks as the minimum supplementation period for the induction of protection against sunburn. In fact, there is a mean increase of the protective effect of β-carotene supplementation in the magnitude of 0.5 standard deviations with every additional month of study duration.

The major source of heterogeneity is the study 10-Lee, and here in particular the data from the 90 mg day^{-1} β-carotene

Table 3. Meta-analysis statistics for each study.

Study name	Standardized mean difference (SMD)	Standard error	Lower limit of 95% confidence interval	Upper limit of 95% confidence interval	Test statistic *z*-value	Test statistic *P*-value
Garmyn *et al.* (9)	−0.1117	0.5404	−1.171	0.9476	0.2067	0.8362
Gollnick *et al.* (10)	0.5967	0.5517	−0.4846	1.6781	1.0816	0.2794
Heinrich *et al.* (11)	1.3386	0.4517	0.4534	2.2239	2.9638	0.003
Lee *et al.* (12)	2.3026	0.5498	1.2249	3.3802	4.1878	0
Mathews-Roth *et al.* (13)	0.3974	0.3806	−0.3487	1.1434	1.044	0.2965
McArdle *et al.* (14)	0	0.5	−0.98	0.98	0	1
Stahl *et al.* (15)	1.1911	0.5425	0.1277	2.2544	2.1954	0.0281
Fixed effects	0.7716	0.185	0.409	1.1342	4.1708	0
Random effects	0.8019	0.3066	0.201	1.4028	2.6155	0.0089

Q-test for heterogeneity: $\chi^2 = 16.05$ on six degrees of freedom ($P = 0.014$).

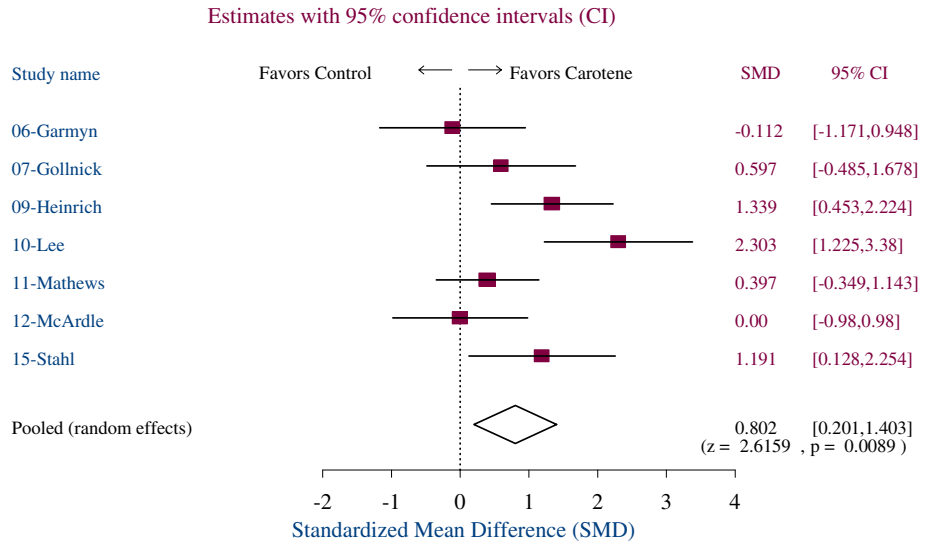

Figure 1. Forest plot for meta-analysis of β-carotene supplementation *vs* placebo on sunburn protection.

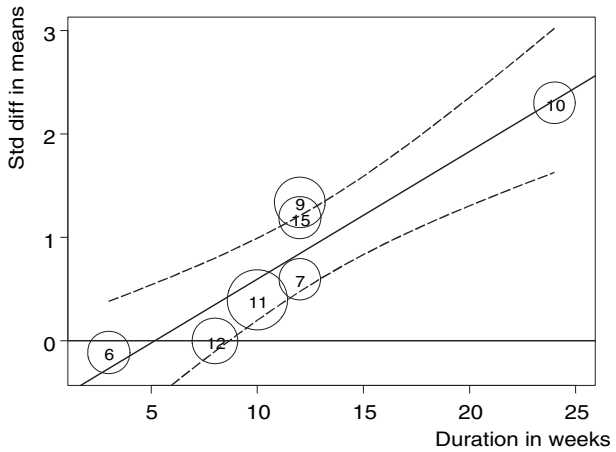

Figure 2. Meta-regression with moderator variable "study duration"—regression line (solid) with 95% confidence intervals (dashed). Circles indicate individual studies.

supplementation. When these data were left out and, instead, only the 60 mg data from this study were used for meta-analysis, the heterogeneity test was no longer significant (Table 4). Under these conditions, the fixed and the random model effects showed very similar and significant effects. In contrast to the first meta-analysis, however, the duration of supplementation was no longer a significant moderator variable ($P = 0.1064$).

DISCUSSION

This meta-analysis indicates that β-carotene supplementation of humans is effective in providing protection against the development of a sunburn reaction. It also demonstrates that achievement of significant protection requires at least 10 weeks of supplementation. This observation emphasizes that systemic photoprotection by β-carotene is quite different from that achieved with a topically applied sunscreen. Whereas proper use of modern sunscreens provides protection against the development of a sunburn reaction within minutes after topical application, β-carotene-induced photoprotection builds only slowly over several weeks of supplementation. Also, sunburn protection provided by a sunscreen can be much stronger than that which is achievable by β-carotene supplementation. Accordingly, sun protection factors of modern sunscreens usually range from 10 to 40

Table 4. Meta-analysis statistics for each study (modified results for study 10-Lee).

Study name	Standardized mean difference (SMD)	Standard error	Lower limit of 95% confidence interval	Upper limit of 95% confidence interval	Test statistic *z*-value	Test statistic *P*-value
Garmyn *et al.* (9)	−0.1117	0.5404	−1.171	0.9476	0.2067	0.8362
Gollnick *et al.* (10)	0.5967	0.5517	−0.4846	1.6781	1.0816	0.2794
Heinrich *et al.* (11)	1.3386	0.4517	0.4534	2.2239	2.9638	0.003
Lee *et al.* (12)	0.9149	0.4482	0.0365	1.7933	2.0415	0.0412
Mathews-Roth *et al.* (13)	0.3974	0.3806	−0.3487	1.1434	1.044	0.2965
McArdle *et al.* (14)	0	0.5	−0.98	0.98	0	1
Stahl *et al.* (15)	1.1911	0.5425	0.1277	2.2544	2.1954	0.0281
Fixed effects	0.6308	0.1799	0.2782	0.9834	3.5064	0.0005
Random effects	0.6296	0.2065	0.2249	1.0343	3.0489	0.0023

Test for heterogeneity: $\chi^2 = 7.78$ on six degrees of freedom ($P = 0.254$).

and can be higher than 90, whereas oral supplementation with β-carotene will yield at best a sun protection factor (SPF) of approximately 4. In other words, sunscreens are the strategy of choice for sunburn prevention if fast and strong protection is required. Obvious disadvantages of sunscreens are (1) that the consumer has to keep in mind to apply the sunscreen prior to sun exposure and (2) that the application has to be done properly, *i.e.* at sufficient amounts in a careful and homogenous manner to all sun exposed skin areas (including those that are difficult to reach), and that even after appropriate application, photoprotection may decrease with time below the indicated SPF, because of a gradual loss of the product from the skin surface due to sweating and mechanical factors. This is in contrast to systemic photoprotection by β-carotene. Once it has been achieved, β-carotene induced photoprotection is (1) always present and (2) homogenously affects the whole skin. Thus, topical application of sunscreens and systemic photoprotection with β-carotene are not competing strategies which are intended to replace each other, but instead they are complementary in nature and should be combined. In this regard, β-carotene intake would serve to provide a basic, all day protection against sunburn, which would affect all parts of the skin, whereas sunscreens would be used "in addition," in particular to prevent sunburns under conditions where the consumer anticipates increased exposure of selected skin areas to UV radiation, *e.g.* during outdoor activities, summer vacations at the beach *etc*. In this regard, a combination of β-carotene with other oral antioxidants should be considered because this may allow to use lower daily doses than those used in the studies mentioned above and thereby improve the safety of daily β-carotene supplementation. This is of particular importance because long-term supplementation with β-carotene in high doses seems to increase the risk for lung cancer in smokers (19).

The precise mechanism(s) through which β-carotene prevents the development of a sunburn reaction in human skin is currently unknown. At least to some extent, UVB-induced skin erythema is due to the formation of reactive oxygen species in irradiated skin and it has therefore been suggested that the well known antioxidative activities of β-carotene account for its photoprotective properties (7). In this regard, it is important to realize that β-carotene resembles natural products such as other carotenoids by being a provitamin A and an excellent singlet oxygen quencher. It is thus tempting to speculate that other natural products with similar properties may exert similar beneficial effects on human skin, under the condition, however, that they—after oral ingestion—resemble β-carotene by reaching the target organ, *i.e.* human skin. At a molecular level, UVB-induced biological effects have been shown to be initiated through three signaling pathways: (1) the formation of DNA photoproducts in nuclear DNA (20), (2) the clustering and subsequent internalization of cell membrane-associated growth factor receptors (21) and (3) the activation of the arylhydrocarbon receptor signaling pathway in the cytoplasm of irradiated human skin cells (21). In addition, these three signaling pathways are closely linked to each other and may partially overlap (22). The efficacy of β-carotene to prevent sunburn formation may thus alternatively be explained by the capacity of β-carotene to interfere with one or several of these signaling pathways.

REFERENCES

1. Lim, H. W. and N. A. Soter (1993) *Clinical Photomedicine*. Marcel Dekker, New York.
2. Gilchrest, B. A. and J. Krutmann (2006) *Skin Aging*. Springer, New York.
3. Lowe, N. J., N. A. Shaath and M. A. Pathak (1997) *Sunscreens*, 2nd edn. Marcel Dekker, New York.
4. Sies, H. and W. Stahl (2004) Nutritional protection against skin damage from sunlight. *Annu. Rev. Nutr.* **24**, 173–200.
5. Afaq, F. and H. Mukthar (2002) Photochemo prevention by botanical antioxidants. *Skin Pharmacol. Appl. Skin Physiol.* **15**, 297–306.
6. Stahl, W. and J. Krutmann (2006) Systemic photoprotection through carotenoids. *Hautarzt* **57**, 281–285.
7. Goralczyk, R. and K. Wertz (2007) Skin photoprotection by carotenoids. In *Health Benefits of Carotenoids, Carotenoids Series*, **Vol. 5** (Edited by G. Britton, H. Pfander and S. Liaanen-Jensen). Birkhäuser, Basel (In press).
8. Eicker, J., V. Kürten, S. Wild, G. Riss, R. Goralczyk, J. Krutmann and M. Berneburg (2003) Betacarotene supplementation protects from photoaging-associated mitochondrial DNA mutation. *Photochem. Photobiol. Sci.* **2**, 655–659.
9. Garmyn, M., J. D. Ribaya-Mercado, R. M. Russell, J. Bhawan and B. A. Gilchrest (1995) Effect of beta-carotene supplementation on the human sunburn reaction. *Exp. Dermatol.* **4**, 104–111.
10. Gollnick, H. P. M., W. Hopfenmüller, C. Hemmes, S. C. Chun, C. Schmid, K. Sundermeier and H. K. Biesalski (1996) Systemic beta carotene plus topical UV-sunscreen are an optimal protection against harmful effects of natural UV-sunlight: Results of the Berlin-Eilath study. *Eur. J. Dermatol.* **6**, 200–205.
11. Heinrich, U., C. Gartner, M. Wiebusch, O. Eichler, H. Sies, H. Tronnier and W. Stahl (2003) Supplementation with beta-carotene or a similar amount of mixed carotenoids protects humans from UV-induced erythema. *J. Nutr.* **133**, 98–101.
12. Lee, J., S. Jiang, N. Levine and R. R. Watson (2000) Carotenoid supplementation reduces erythema in human skin after simulated solar radiation exposure. *Proc. Soc. Exp. Biol. Med.* **223**, 170–174.
13. Mathews-Roth, M. M., M. A. Pathak, J. A. Parrish, T. B. Fitzpatrick, E. H. Kass, K. Toda and W. Clemens (1972) A clinical trial of the effects of oral beta-carotene on the responses of human skin to solar radiation. *J. Invest. Dermatol.* **59**, 349–353.
14. McArdle, F., L. E. Rhodes, R. A. Parslew, G. L. Close, C. I. A. Jack, P. S. Friedmann and M. J. Jackson (2004) Effects of oral vitamin E and beta-carotene supplementation on ultraviolet radiation-induced oxidative stress in human skin. *Am. J. Clin. Nutr.* **80**, 1270–1275.
15. Stahl, W., U. Heinrich, H. Jungmann, H. Sies and H. Tronnier (2000) Carotenoids and carotenoids plus vitamin E protect against ultraviolet light-induced erythema in humans. *Am. J. Clin. Nutr.* **71**, 795–798.
16. Hedges, L. V. and I. Olkin (1985) *Statistical Methods for Meta-Analysis*. Academic Press, San Diego.
17. Normand, S. L. T. (1999) Meta-analysis: Formulating, evaluating, combining, and reporting. *Statist. Med.* **18**, 321–359.
18. van Houwelingen, H. C., L. R. Arends and T. Stijnen (2002) Advanced methods in meta-analysis: Multivariate approach and meta regression. *Statist. Med.* **21**, 589–624.
19. Albanes, D., O. P. Heinonen, P. R. Taylor, J. Virtamo, B. K. Edwards, M. Rautalahti, A. M. Hartman, J. Palmgren, L. S. Freedman, J. Haapakoski, M. J. Barrett, P. Pietinen, N. Malila, E. Tala, K. Liippo, E. R. Salomaa, J. A. Tangrea, L. Teppo, F. B. Askin, E. Taskinen, Y. Erozan, P. Greenwald and J. K. Huttunen (1996) Alpha-tocopherol, beta-carotene cancer prevention study: Effects of base-line characteristics and study compliance. *J. Natl Cancer Inst.* **88**, 1560–1570.

20. Stege, H., L. Roza, A. A. Vink, M. Grewe, T. Ruzicka, S. Grether-Beck and J. Krutmann (2000) Enzyme plus light therapy to repair DNA damage in ultraviolet-B-irradiated human skin. *Proc. Natl. Acad. Sci. USA* **97**, 1790–1795.
21. Kulms, D., B. Pöppelmann, D. Yarosh, T. A. Luger, J. Krutmann and T. Schwarz (1999) Nuclear and cell membrane effects contribute independently to the induction of apoptosis in human cells exposed to UVB radiation. *Proc. Natl Acad. Sci. USA* **96**, 7974–7979.
22. Fritsche, E., C. Schäfer, C. Calles, T. Bernsmann, T. Bernhausen, M. Wurm, U. Hübenthal, J. E. Cline, H. Hajimiragha, P. Schroeder, L. O. Klotz, A. Rannug, P. Fürst, H. Hanenberg, J. Abel and J. Krutmann (2007) Lightening up the UV response by identification of the arylhydrocarbon receptor as a cytoplasmic target for ultraviolet radiation. *Proc. Natl Acad. Sci. USA* **104**, 8851–8856.