Carotenoids and Prostate Cancer Risk

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Abstract: Chemoprevention is presumably one of most effective means to combat prostate cancer (PCa). Patients usually require more than a decade to develop a clinically significant Pca, therefore, an ideal target for chemoprevention. This review will focus on recent findings of a group of naturally occurring chemicals, carotenoids, for potential use in reducing PCa risk.

Key Words: Prostate cancer, chemoprevention, carotenoids, retinoids, carotene, lycopene, antioxidant, cancer risk.

INTRODUCTION

Prostate cancer (PCa) is the second leading cancer killer, next to lung cancer, in male population of many highly developed countries including USA, UK and others. Inspiration from low PCa incidence in Asian countries and evidence from the more recent epidemiologic studies, nutrition and diet may indeed impact PCa as well as other types of cancer risk. It has been strongly suggested that chemoprevention would be a highly effective means to combat this disease due to its high incidence, long latency of becoming clinically significant cancer and disease-related morbidity and mortality [1-6]. It has been suggested that proper diets may eventually reduce 50-60% incidence of many types of cancer [1, 5, 6].

This review will concentrate on a class of phytochemicals, carotenoids, for their effects in prevention of Pca. Carotenoids are unique constituents of a healthy diet in which they may play an important role in the network of antioxidant vitamins and phytochemicals, therefore beneficial in preventing many human diseases including cancers. Some of carotenoids may be viewed as pro-vitamin A because they can be converted to vitamin A or retinoids after consumed and absorbed by the body. However, this review will mainly focus on carotenoids. In some cases, retinoids may be also discussed side by side with carotenoids.

TYPES OF CAROTENOIDS AND THEIR DISTRIBUTION IN DIETS

Up to now, there are at least 500-600 different carotenoids being identified [7-9]. Carotenoids are fat-soluble tetraterpenoids, most of which contain a central carbon chain of alternating single and double bonds with different cyclic or acyclic end groups. The double bonds may show an array of *cis*/*trans* (E/Z) configurations in a given carotenoid [7-9]. It has been shown that the all-*trans* form is thermodynamically most stable and predominant in nature but several *cis* isomers of carotenoids can be detected in blood and tissues [10, 11]. Although carotenoids can be found in animals and plants, they are only synthesized in plants and some microorganisms including bacteria, yeasts, and molds. The major forms of carotenoids in plant foods and other food products are shown in Fig. **1** and Table **1**. Animals and humans can not synthesize carotenoids *de novo*, thus depending on dietary supply. Carotenoids may be divided into two main groups, i. e., carotenes and xanthophylls [7]. β-Carotene, α-carotene, and lycopene are important members of the carotene group composed only of carbon and hydrogen atoms. The major xanthophylls including zeaxanthin, lutein, α-and β-cryptoxanthin, canthaxanthin and astaxanthin carry at least one oxygen atom. Note, because xanthophylls contain at least one hydroxyl group, they are more polar than carotenes. Moreover, as mentioned above some carotenoids, viewed as pro-vitamin A, can be converted to vitamin A or retinoic acid, including α-carotene, β-carotene and β-cryptoxanthin [7, 9]. The conversion of pro-vitamin A carotenoids like β-carotene to retinal can occur in the small bowel mucosa and in the liver by β,β -carotene 15,15' monooxygenase (previously termed beta-carotene 15,15' dioxygenase) at center of the carotene. Retinal can be further reduced by retinal resductase to retinol [8-13]. Another enzyme was found to be able to catalyze an eccentric cleavage of carotenoids into apo-carotenoids and retinal [9, 10, 12, 13]. Although retinoids possess anti-cancer activity, the non-pro-vitamin A carotenoids (e.g., lycopene) also possess anti-cancer activity as demonstrated in laboratory tests and experimental models of cancer and have been associated with lower cancer risk in epidemiological studies [1, 3, 9, 13]. As mentioned above there are a relatively large number of carotenoids in natural source, however, only approximately 50 of them are present in common vegetables and fruits in US diets [8-10]. Finally, perhaps just over a dozen of these carotenoids or their metabolites can be detected in human blood and tissues which may be attributed to human health [8, 13].

Among carotenoids, lycopene has drawn a heavy attention to its potential role responsible for benefits to preventing chronic diseases including PCa by consumption of tomato or tomato products [1, 3, 8, 9, 13]. Interesting aspect is that the prostate is one of preferential tissues to accumulate lycopene

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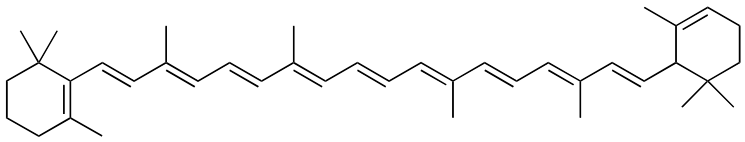
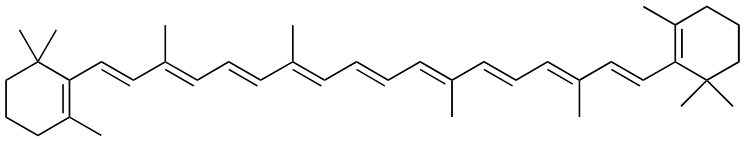
A. Dietary Carotenoids

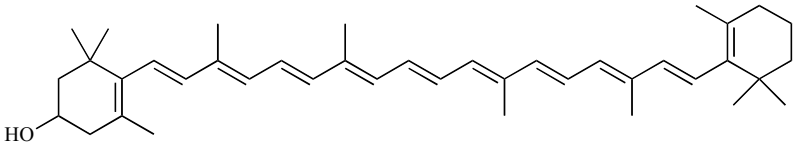
α-Carotene



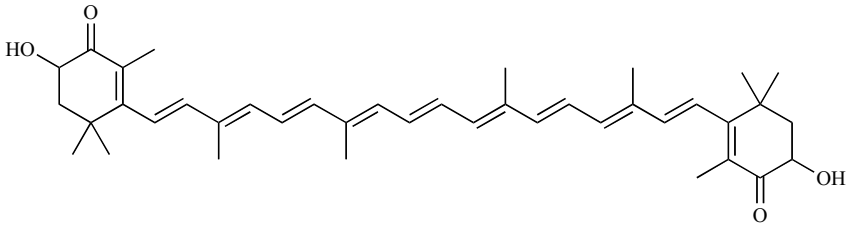
β-Carotene



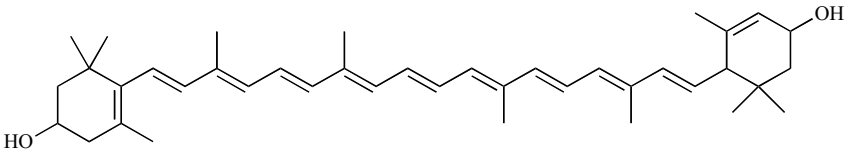
β-Cryptoxanthin



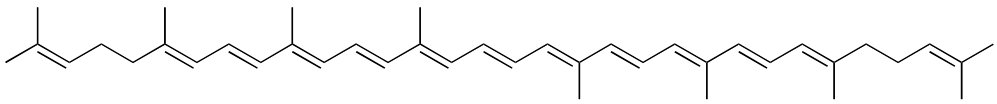
Fucoxanthin



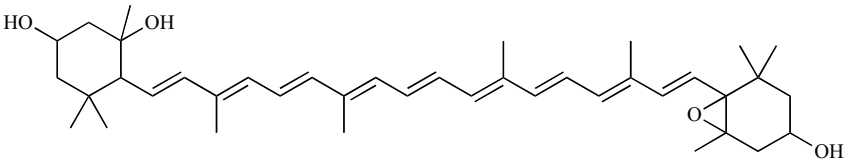
Lutein



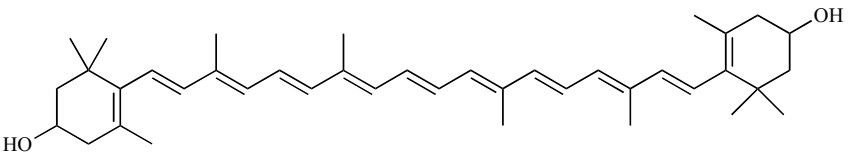
Neoxanthin



Lycopene



Zeaxanthin



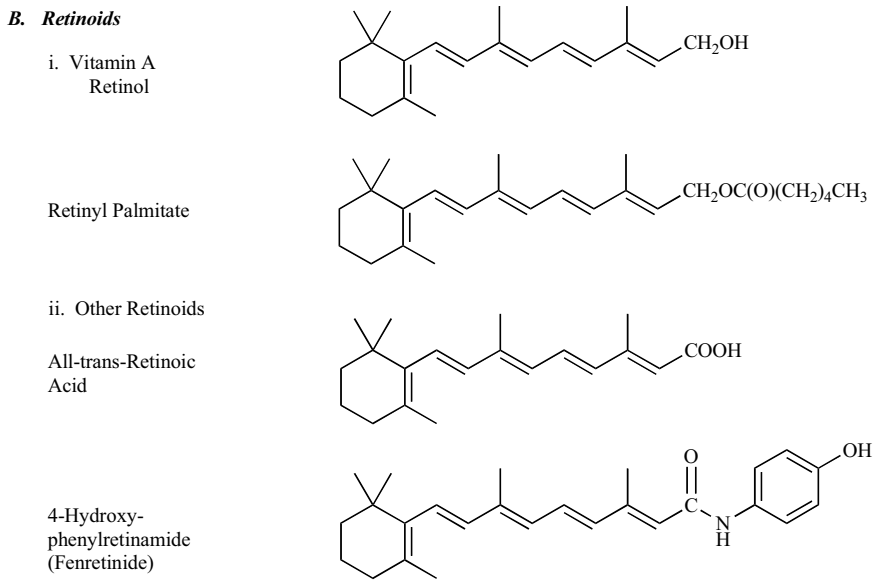


Fig. (1). Chemical structures of some common carotenoids and retinoids.

and this preference is more towards malignant than benign prostate [14, 15]. Also lycopene detected in the prostate is predominantly cis-forms while mainly all-trans form lycopene is present in plant foods [14, 16-18]. Further studies will be required to clarify the bioactivity of isoforms of lycopene in their anti-prostate cancer action. Recently, it has been proposed that *in vivo* lycopene metabolites or oxidation products such as apo 10'-lycopenic acid, 2,7,11-trimethyltetradecahexaene-1,14-dial are also bioactive against cancer development [15].

MECHANISMS OF ANTI-PROSTATE CANCER ACTIVITIES OF CAROTENOIDS

Antioxidant Activities

Excessive reactive oxygen (ROS) and nitrogen species (RNS) can be produced during aerobic metabolism and pathological processes and then cause damages in cellular lipids, DNA or proteins [13, 19, 20]. Carotenoids are usually involved in the scavenging of two types of the ROS, singlet molecular oxygen ($^1O_2$), and peroxyl radicals. Carotenoids can directly transfer excitation energy from $^1O_2$ and generates ground state oxygen and an excited triplet state carotenoid, which further transform the energy into heat and the ground state intact carotenoid [9, 11, 21, 22]. The potency of this kind of quench effects is closely related to the number of conjugated double bonds of a given carotenoid, thus lycopene is the top quencher among carotenoids. Carotenoids like lycopene can also trap other ROS and RNS, like $OH^{\surd}$, $NO_2^{\surd}$ or peroxynitrite, however, leading to oxidative breakdown of the carotenoid molecules [20, 23-26]. This action seems to suggest that the carotenoids may act in the front line of defense. It has been demonstrated that lycopene can reduce oxidative DNA damage in cell cultures and in rats *in vivo* [27, 28]. Also, human studies showed that tomato consumption could protect human leukocytes against oxidative DNA damage [29-31]. Additional study [32] showed that lycopene-rich tomato sauce consumption could reduce oxidative DNA damage in human prostate.

Interestingly, it has been suggested that when two structurally different antioxidant compounds are mixed together, they can generate synergistic protection activity against increased oxidative stress [8, 9]. By pairing a number of carotenoids in a multilamellar liposomes assay system for protection of oxidative damage, it was found that the pairing of other carotenoids or vitamin E with lycopene or lutein produced the most profound synergistic effect [33]. Among many individual antioxidants, vitamins E, C and β-carotene exhibit cooperative synergistic effects scavenging RNS [34, 35]. A cooperative interaction between α-tocopherol and β-carotene can be observed in a membrane model [36], showing a synergistic inhibitory effect of lipid peroxidation. The synergistic protection effect may be related to the specific positioning of different carotenoids and other lipophilic antioxidants in membranes [37]. It has been observed that lycopene at its physiological concentrations (less than 1 uM) can effectively inhibit prostate cancer cell proliferation when only the presence of physiological concentrations (50 uM) of alpha-tocopherol, but not with beta-tocopherol, ascorbic acid or probucol [38]. Similar results [39] were also obtained in xenograft of human prostate cancer cell line PC-3 in nude mice in which a daily dose of lycopene (5 or 50 mg/kg body weight), alpha-tocopheryl acetate (5 or 50 mg/kg body weight), a mixture of both, or vehicle was given. The results demonstrated that only the combined treatments of lycopene and vitamin E could significantly repress orthotopic tumor growth by 73% at day 42 as well as increase median survival time by 40% from 47 to 66 days. Furthermore, rat MatLyLu Dunning prostate tumor [40] was used to address the *in vivo* action of lycopene and vitamin E. Diet supplementation for 4 weeks with 200 ppm lycopene, and 540 ppm vitamin E was applied to rats receiving the tumor cells orthotopically in the prostate. After 14 days tumor cell injection, tumor growth

Table 1. Major Carotenoids (µg/100g Edible Portion) in Some Vegetables, Fruits and Food Products

	α-Carotene	β-Carotene	β-Cryptoxanthin	Lutein and Zeaxanthin	Lycopene
Apples raw with skin	30	-	-	-	-
Apricots	-	6,640	-	-	65
Asparagus, raw	12	493	-	-	-
Avacados raw	28	53	56	-	-
Bananas	5	21	-	-	-
Bean, snap, green, raw	68	377	-	640	-
Blueberries, raw	-	35	-	-	-
Broccoli, raw	1	779	-	2,445	-
Cabbage, raw	-	65	-	310	-
Carrots, baby, raw	4,425	7,275	-	358	-
Carrots, raw	4,649	8,836	-	-	-
Celery, raw	-	150	-	232	-
Cherries, sweet, raw	-	28	-	-	-
Corn, canned	33	30	-	884	-
Grapefruit, raw, pink, red	5	603	12	12	1,462
Kale, raw	-	6,202	-	15,798	-
Lettuce, romaine, raw	-	1,272	-	2,635	-
Mangos, raw	17	445	11	-40	-
Melons, cantaloupe, raw	27	1,595	-	36	-
Orange juice, raw	2	4	15	187	-
Orange, raw	16	51	122	75	-
Papayas, raw	-	276	761	-	-
Peas, green frozen	33	320	-	-	-
Peppers, sweet, green, raw	22	198	-	-	-
Peppers, sweet, red raw	59	2,379	2,205	-	-
Pumpkin, canned, no salt	4,795	6,940	-	-	-
Spinach, raw	-	5,597	-	11,938	-
Tomato, red, ripe, raw	112	393	-	130	3,025
Tomato juice, canned	-	428	-	60	9,318
Watermelon, raw	-	295	103	17	4,868
Beef, variety meats	-	621	-	-	-
Butter	-	158	-	-	-

(Table 1. Contd….)

	α-Carotene	β-Carotene	β-Cryptoxanthin	Lutein and Zeaxanthin	Lycopene
Cheese, cheddar	-	85	-	-	-
Egg, whole, raw	-	-	-	55	-
Margarine, regular	-	485	-	-	-
Sauce, pasta	-	440	-	160	15,990
Soup, vegetarian, vegetable, canned, condensed, commercial	410	1,500	-	160	1,930
Soup, vegetable beef, canned, condensed, commercial	489	1,618	-	2	364

"-" : not available or not detectable; Adopted from (Database, 1998 Database, U.-N.C. 1998. USDA-NCC Carotenoid Database for US Foods-1998. Available from: <www.nal.usdea.gov/fnic/foodcomp/Data/car98/car98.html>).

as examined by magnetic resonance imaging showing a significant increase in necrotic area only in rats treated with both vitamin E and lycopene. Gene profiling analysis demonstrated that lycopene and vitamin may repress both prostatic anrdrogen signaling pathways and prostatic expression of interleukin 6 and insulin like growth factor-1 (IGF-1), therefore, interfering with internal autocrine or paracrine regulatory pathways for prostate tumor growth. Later, the same group of the authors [41] showed lycopene can reduce local prostatic androgen signaling, IGF-I expression, and basal inflammatory signals in normal rat prostate tissue, when young rats administered with 200 ppm lycopene in diet for up to 8 weeks. Although these studies showed the specific *in vivo* gene regulation targets by lycopene, it is still not clear if the action of lycopene is directly derived from its anti-oxidant activity.

Another related antioxidant mediated anticancer activity of carotenoids is their potential of increase of antioxidant enzymes and detoxifiying enzymes [42]. However, the data varies in different experiments. A study by Gradelet *et al*., [43] was designed to investigate if carotenoids such as canthaxanthin, astaxanthin, lycopene and lutein can alter liver drug metabolizing enzymes in male rats. The results showed after 15 days of feeding with diets containing each those carotenoids, canthaxanthin and astaxanthin indeed increased the liver content of P450, and the activities of NADH- and NADPH-cytochrome c reductase. However, lycopnene and lutein showed very little effect. Further, Breinholt *et al*., [44] treated female rats with lycopnene at concentrations from 0.001 to 0.1 g/kg body weight/day for 2 weeks and examined alteration of drug-metabolizing (benzyloxyresorufin O-dealkylase, ethoxyresorufin O-dealkylase, hepatic quinone reductase and glutathione transferase) and antioxidant enzyme (superoxide dismutase, glutathione reductase and glutathione peroxidase) levels. The authors concluded that lycopene can enhance, although not particularly high, those enzyme activities in rat which might be relevant to the protective effects of lycopnene against human cancer. An earlier *in vitro* study [45] using Colo205 colon cancer cells showed lycopene and beta-carotene had no effect on levels of NAD(P)H:quinone reductase (QR) and GST although retinol and retinoic acid could stimulate QR activity.

Recently it has been shown [46] that carotenoids tested, especially lycopene may up-regulate phase II detoxification enzymes through activation of Nrf2 transcription factor and its binding to the antioxidant response element (ARE) of phase II detoxification enzyme genes. The study showed that lycopene induced an increase of the phase II enzymes NAD (P)H:quinone oxidoreductase and gamma-glutamylcysteine synthetase at mRNA and protein levels in human cancer cell lines tested. Further experiments [46] showed that the antioxidant actitvity of the carotenoids is not directly related to their induction ability of the phase II enzymes.

Biological Functions other than Antioxidant Activities

Non-provitamin A cartenoids and retinoids may cause cell cycle retention with which IGF-I receptor signaling was diminished as well as cyclin D levels and phosphorylation of the retinoblastoma protein [47, 48] were reduced. Many biological effects pertinent to anticancer potentials of carotenoids including cell cycle/proliferation/apoptosis, cell communication and others might not totally rely on their primary antioxidant function, additional mechanisms may play a role. For example, the study in the rat system described in the above section seemed to indicate part of lycopene's anti PCa activities may not be associated with its antioxidant activity. Recently, Kotake-Nara *et al*., [49] compared 15 carotenoids for their antiproliferation effects on three human PCa cell lines and concluded that phytofluene, zeta-carotene and lycopene but not phytoene, canthaxanthin, beta-cryptoxanthin and zeaxanthin could significantly affect the growth of the PCa cells. In addition, the authors [50] found that neoxanthin and fucoxanthin, rich mainly in spinach and edible brown algae, respectively, are more effective than other carotenoids tested in anti-proliferation activity of three human PCa cell lines. These two carotenoids could decrease

the expression of Bax and Bcl-2 proteins and induced apoptosis *via* caspase 3 activation.

Retenoids in our body system are obtained from provitamin A carotenoids or preformed retinoids whose biological functions including anti-cancer effects are mainly mediated *via* two classes of nuclear receptor family, i.e., retinoic acid receptors (RARs) alpha, beta, gamma and retinoid X receptors (RXRs) alpha, beta, gamma [42, 51]. All-trans-retinoic acid and the isomer 9-cisretinoic acid are ligands for RARs and RXRs, respectively. The activation of the receptors by their ligands can therefore, exert cell proliferation and differentiation. In addition, there are several hundred of structurally unrelated, synthetic retinoids exhibiting similar effects. Retinoids have been suggested to play a role in regulation of prostate growth and differentiation [51, 52, 53]. Deficiency in vitamin A can affect some early development of the prostate as also shown in the mouse knockouts of RAR gamma with metaplasia and keratinization [53]. The RAR gamma knockout [53] (Lohnes *et al*., 1993) showed prostatic lumen defect in secretion. In laboratory studies, retinoids alone or with other agents such as vitamin D [54], can cause cell cycle arrest, inhibit PCa proliferation or induce apoptosis as well as suppress prostate carcinogenesis [51]. Retinoids may down-regulate anti-apoptotic Bcl2 and upregulate RAR beta and tissue transgluaminase in PCa cells [55]. Retinoic acid was also shown to inhibit the function of the androgen receptor [56]. Recently, epigenetic events such as promoter DNA hypermethylation have been frequently observed in many cancers including PCa and have been suggested to be involved in carcinogenesis. RARbeta2 is one of frequently methylated genes whose expression is abnormally lowered in malignant cells compared to the normal counterparts [57, 58]. Whether this indicates the role of RARb2 in prostate carcinogenesis or cancer progression is not clear. Furthermore, whether reactivation of RARb2 expression by demethylating agents (e.g., 5'aza-deoxycytidine) [58, 59, 60] in combination with use of retinoids can enhance the efficacy for PCa treatment may be worth an investigation.

It has been shown that both retinoids and non-provitamin A carotenoids can increase levels of a gap junctional communication (GJC) protein connexin 43 (Cx43) in several cancer cells [61-64]. Gap junctions that allow exchange of low molecular cellular components (< 1000 Da) between neighboring cells seem to be critical for maintaining normal cell phenotype [61-63]. Although the mechanisms are not well understood, GJC is implicated in controlling cell proliferation, differentiation and apoptosis. Malignant cells are usually deficient in GJC [65, 66]. Restoration of GJC proteins may resume some features of normal cell phenotype and repress cell transformation. Thus, GJC proteins or connexin family proteins may be viewed as tumor suppressors. Experiments were also performed and found that there was no correlation between the antioxidant capacity of carotenoids tested and the ability of increase in GJC proteins, suggesting that the antioxidant activities of carotenoids was not related to their effect on regulating GJC proteins [1, 67, 68]. In clinical trials, applying high doses of supplemental lycopene to PCa patients for 3 weeks prior to radical prostatectomy appeared to increase expression of Cx43 and decreased pathological severity of treated versus control group [69]. Similar studies were performed to show the potential benefits of lycopene to improve clinical parameters in PCa patients [70, 71]. However, in an *in vitro* study showed lycopene failed to inhibit cell prolifration and to increase expression of Cx43 in a highly meatstatic PC-3 subline [72, 73]. Whether this can implicate the *in vivo* heterogenecity of clonal PCa cells that can arise to lycopene resistance remains to to be determined.

Both retinoids and carotenoids up-regulate connexin mainly at the transcriptional levels [1, 63, 68]. However it seems that retenoids but not non-provitamin A carotenoids (e.g., beta carotene, astaxanthin and lycopene) activate connexin *via* RARs, because RAR antagonists showed to block retinoid induced connexin expression at the transciptional and protein levels. The aforementioned non-provitamin A carotenoids have very little affinity to RARs or RXRs. In contrast, peroxisome proliferator activated receptor (PPAR) antagonist GW9662 could only block activation of connexin expression by carotenoids but not retinoids [67]. Whether the non provitamin A carotenoids can directly bind the PPAR remains to be addressed. However, it has been proposed [1, 68] that there are separate mechanisms to mediate the regulation of the connexin 43 gene expression by carotenoids or retinoids. Moreover, by transfection assays the responsive region of the connexin 43 gene promoter to both retinoids and the carotenoids was found within -158 bp and +209 bp of the transcription start site of the gene. Intriguingly this region contains no regular canonical RAR or PPAR response element but a Sp1/Sp3 GC-box. It certainly requires more studies to unravel the actual regulatory mechanisms used by the non-provitamin A carotenoids and the retinoids.

DEMONSTRATION OF ANTI-PROSTATE CANCER ACTIVITIES IN HUMAN STUDIES

An early study [74] investigated the relationship of diet and life style with PCa risk in a cohort of approximately 14,000 Seventh-day Adventist men who completed a detailed lifestyle questionnaire in 1976. For a 6-year follow-up, 180 histologically proven PCa were detected. One important finding was that increasing consumption of tomatoes and other fruits and vegetables was significantly associated with decreased PCa risk. Subsequently, the US Health Professionals Follow-up Study (HPFS) [75] showed there was an inverse association between high intake of tomato products and PCa risk. This study suggested that lycopene intake from tomato-derived products but not the overall intake of fruits and vegetables was associated with lowered PCa risk. The same latter investigator group conducted another analysis of the HPFS from yr1986 to 1998 consisting of 47,365 participants with 2481 men being developed PCa [76]. Although the study showed an association of lycopene and frequent consumption of tomato products with reduced PCa, the authors did acknowledge the degree of the inverse association was moderate so that a small study or one with improper assessment would miss the significance. Another more recent case-control nested analysis of the same HPFS [77] with 450 matched PCa men showed modest inverse, but not statistically significant, associations of PCa risk with plasma levels of a-carotene, beta-carotene, and lycopene. However, there was a statistically significant inverse association between higher plasma lycopene levels and lower risk of PCa

in a sub group of men with older age or whose family history showed no PCa. On the other hand, regarding the protective effects of dietary or supplemental carotenoids, many observational epidemiological or clinical studies produced inconsistent results. For example, there were a few large clinical trials [78-81] as well as an observantional study with American Japanese in Hawaii [82] indicating no obvious association of beta-carotene supplementation or serum carotenoid levels with PCa risk. Yet, more recently, a relatively small case-control study with 118 non-Hispanic Caucasian with nonmetastatic PCa and 52 healthy men mainly from southeast Texas was conducted to evaluate associations between cancer risk and plasma levels of total carotenoids and several types of carotenoids [83]. The conclusion of the study suggested that higher circulating levels of alpha-cryptoxanthin, alpha-carotene, trans-beta-carotene, lutein and zeaxanthin as well as cis-lycopene isomer 1 but not total lycopenes, or other lycopene isoforms could contribute to lower PCa risk. In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial with 1338 cases of PCa among 29361 men for a 8 years follow-up [84], it was concluded that there was no overall association of PCa risk with intake of beta-carotene and other anti-oxidants. Similar conclusion was obtained for lycopene or tomato products [85]. More recent analysis of the same study [86] indicated that high serum beta-carotene may be associated with increased risk of aggressive prostate cancer. However, it was suggested that high supplemental beta-carotene intake at at least 2000 mu g/day was associated with reduced risk of the cancer only in men with low dietary beta-carotene intakes. Another case-control study of diet and PCa in western New York with 433 men with primary, PCa and 538 population-based controls [87] also revealed similar results in that only those men in the highest quartile of intake of beta-carotene, alpha-carotene, lutein, and lycopene and other phytocompounds showed reduced PCa risk when compared to men in the lowest quartile of intakes.

As already mentioned above in human studies as well as in many *in vitro* laboratory tests and animal studies, lycopene may be the one showing more promising role in preventing PCa than other carotenoids since it shows more consistent results in human studies [3] although there were some conflicting results existed [88]. Evaluating most of the studies we can still strongly argue that, overall, carotenoids especially lycopene may have protection effect against PCa development or progression. Clearly more accurate information of the carotenoid content of foods and amounts of relevant food consumption as well as absorption, metabolic, genetic and epigenetic factors of participant individuals in studies that could complicate the interpretation of results or act as confounding factors should be included, clarified or minimized in order to improve the evaluation.

POTENTIAL HARMS OF USE OF CAROTENOIDS IN CANCER PREVENTION

Although there are still some debates about if higher intake of fruits and vegetables is more effective than use of supplements of dietary compounds in cancer prevention, little evidence showed higher intake of fruits and vegetables can increase cancer risk. However, recent studies [80, 81, 89, 90] indicated that tobacco may interact with isolated forms of carotenoids and produced unexpected effects--increasing cancer risk. A double-blind, placebo-controlled trial, the Alpha-Tocopherol-Beta-Carotene (ATBC) trial [89], was performed to demonstrate anti-cancer effects of two anti-oxidants, beta-carotene and vitamin E, With 29,133 male smokers receiving a daily supplement of either 20 mg of beta-carotene or 50 mg of vitamin E, both, or a placebo for a 5 to 8 year follow up, the partipicipants receiving beta-carotene had a statistically significantly higher lung cancer risk than did men who only received placebo. The intake of beta-carotene also increased the mortality from cardiovascular disease in the same study. Later, the Carotene and Retinol Efficacy Trial (CARET) [80, 81] was designed to use beta-carotene with retinol for lung cancer prevention in men and women smokers and/or asbestos workers. The study also showed similar results that lung cancer risk was statistically significantly increased in active heavy smokers. There are other studies [91-93] showed similar results in which high intake of beta-carotene can increase cancer risk in active heavy active smokers but may benefit or neutral to those never smokers. Human and animal studies showed [91, 94-98], indeed, carotene may have interaction with tobacco metabolites, the actual mechanism(s) involved is still poorly understood. However, so far, there is no indication if lycopene can enhance cancer risk in smokers yet. Although whether tobacco use can increase PCa risk is still not entirely clear and requires more studies to clarify it. Nonetheless, certain awareness needs to keep in mind that smokers should avoid the use of high dose carotenoid supplements for cancer prevention.

CONCLUSIONS

According to a variety of studies shown in the literature, carotenoids including carotenes and lycopene seem to be promising dietary compounds for reducing PCa risk. Neoxanthin and fucoxanthin may be new promising chemopreventive carotenoids for PCa that require more extensive studies in the near future. Whether that tobacco use can increase PCa risk and carotenoids can further enhance the tobacco effects on PCa is not certain at presnt time, precaution should be taken when isolated carotenoids as diet supplements are considered to be chronically used for disease or PCa prevention purposes.

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REFERENCES

[1] Bertram, J.S.; Vine, A.L. *Biochim. Biophys. Acta,* **2005**, *1740,* 170.
[2] Brand,T.C.; Canby-Hagino, E.D.; Pratap Kumar, A.; Ghosh, R.; Leach R.J.; Thompson, I.M. *Hematol. Oncol. Clin. North Am*., **2006**, *20,* 831.
[3] Chan, J.M.; Gann, P.H.; Giovannucci, E.L. *J. Clin. Oncol.,* **2005**, *23,* 8152.
[4] Khan, N.; Afaq, F.; Saleem, M.; Ahmad, N.; Mukhtar, H. *Cancer Res.,* **2006**, *66,* 2500.
[5] Klein, E.A. *Ann. Rev. Med.,* **2006**, *57,* 49.
[6] Lippman, S.M.; Lee, J.J. *Cancer Res.,* 2006, *66,* 2893.
[7] Olson, J.A.; Krinsky, N.I. *FASEB J.,* **1995**, *9,* 1547.
[8] Shixian, Q.; Dai, Y.; Kakuda, Y.; Shi, J.; Mittal, G.; Yeung, D.; Jiang, Y. *Food Rev. Internl.,* **2005**, *21*, 295.

[9] Stahl, W.; Sies, H. *Biochim. Biophys. Acta,* **2005**, *1740,* 101.
[10] Khachik F. *Pure Appl. Chem.,* **2006**, *78,*1551.
[11] Stahl, W.; Sies, H. *Mol. Aspects Med.,* 2003, *24***,** 345.Stahl, W.; Sundquist, A.R.; Hanusch, M.; Schwarz, W.; Sies, H. *Clin. Chem.,* **1993**, *39,* 810.
[12] Borel, P.; Drai, J.; Faure, H.; Fayol, V.; Galabert, C.; Laromiguiere, M.; Le Moel, G. *Ann. Biol. Clin. (Paris),* **2005**, *63,* 165.
[13] Krinsky, N.I.; Johnson, E.J. *Mol. Aspects Med.,* **2005**, *26,* 459.
[14] Erdman, J.W. Jr. *J. Nutr.,* **2005**, *135***,** 2046S.
[15] Lindshield , B.L.; Canene-Adams, K.; Erdman, J.W. Jr. *Arch. Biochem. Biophys.,* **2007**, *458*,136.
[16] Clinton, S.K.; Emenhiser, C.; Schwartz, S.J.; Bostwick, D.G.; Williams, A.W.; Moore, B.J.; Erdman, J.W. *Cancer Epidemiol. Biomark. Prev.,* **1996**, *5,* 823.
[17] Kaplan, L.A.; Lau, J.M.; Stein, E.A. *Clin. Physiol. Biochem.,* **1990**, *8,* 1.
[18] Yeum, K.-J.; Booth, S.; Sadowski, J.; Lin, C.; Tang, G.; Krinsky, N.I.; Russell, R.M. *Am. J. Clin. Nutr.,* **1996**, *64***,** 594.
[19] Halliwell, B. *Ann. Rev. Nutr.,* **1996**, *16,* 33.
[20] Mortensen, A.; Skibsted, L.H.; Truscott, T.G. *Biochem. Biophys.,* **2001**, *385,* 13.
[21] Conn, P.F.; Schalch, W.; Truscott, T.G. *J. Photochem. Photobiol. B Biol.,* **1991**, *11***,** 41.
[22] Schmidt, R. *J. Phys. Chem.,* **2004**, *108***,** 5509.
[23] Pannala, A.S.; Rice-Evans, C.; Sampson, J.; Singh, S. *FEBS Lett.,* **1998**, *423,* 297.
[24] Sies, H. *Eur. J. Biochem.,* **1993**, *215***,** 213.
[25] Wertz, K.; Siler, U.; Goralczyk, R. *Arch. Biochem. Biophys*., **2004**, *430,* 127.
[26] Woodall, A.A.; Britton, G.; Jackson, M.J. *Biochim. Biophys. Acta,* **1997**, *1336,* 575.
[27] Matos, H.R.; Di Mascio, P.; Medeiros, M.H. *Arch. Biochem. Biophys.,* **2000**, *383,* 56.
[28] Matos, H.R.; Capelozzi, V.L.; Gomes, O.F.; Mascio, P.D.; Medeiros, M.H. *Arch. Biochem. Biophys.,* **2001**, *396,* 171.
[29] Pool-Zobel, B.L.; Bub, A.; Muller, H.; Wollowski I.; Rechkemmer, G. *Carcinogenesis,* **1997**, *18,* 1847.
[30] Porrini M.; Riso. P. *J. Nutr.,* **2000**, *130,* 189.
[31] Rehman, A.; Bourne, L.C.; Halliwell, B.; Rice-Evans, C.A. *Biochem. Biophys. Res. Commun.,* **1999**, *262,* 828.
[32] Bowen, P.; Chen, L.; Stacewicz-Sapuntzakis, M.; Duncan, C.; Sharifi, R.; Ghosh, L.; Kim, H.S.; Christov-Tzelkov, K.; van Breemen, R. *Exp. Biol. Med. (Maywood),* **2002**, *227,* 886.
[33] Stahl, W.; Junghans, A.; de Boer, B.; Driomina, E.S.; Briviba, K.; Sies, H. *FEBS Lett.,* **1998**, *427,* 305.
[34] Böhm, F.; R. Edge, R.; Lange L.;Truscott, T.G. *J. Photochem. Photobiol. B Biol.,* **1998**, *44***,** 211.
[35] Böhm, F.; Edge, R.; McGarvey, D.J.; Truscott, T.G. *FEBS Lett.,* **1998**, *436***,** 387.
[36] Palozza, P.; Krinsky, N.I. Beta-carotene and alpha-tocopherol are synergistic antioxidants, *Arch. Biochem. Biophys.,* **1992**, *297***,** 184.
[37] Heber, D,; Lu, Q.Y. *Exp. Biol. Med. (Maywood),* **2002**, *227,* 920.
[38] Pastori, M.; Pfander, H.; Boscoboinik, D.; Azzi, A. *Biochem. Biophys. Res. Commun.,* **1998**, *250,* 582.
[39] Limpens, J.; Schroder, F.H.; de Ridder, C.M.; Bolder, C.A.; Wildhagen, M.F.; Obermuller-Jevic, U.C.; Kramer K, van Weerden WM. *J. Nutr.,* **2006**, *136,* 1287.
[40] Siler, U.; Barella. L.; Spitzer, V.; Schnorr, J.; Lein, M.; Goralczyk, R.; Wertz, K. *FASEB J.,* **2004**, *18,* 1019.
[41] Herzog, A.; Siler, U.; Spitzer, V.; Seifert, N.; Denelavas, A.; Hunziker, P.B.; Hunziker, W.; Goralczyk, R.; Wertz, K. *FASEB J.,* **2005**, *19,* 272
[42] Sharoni, Y.; Danilenko, M.; Dubi, N.; Ben-Dor, A.; Levy, J. *Arch. Biochem. Biophys.,* **2004**, *430,* 89.
[43] Gradelet, S.; Astorg, P.; Leclerc, J.; Chevalier, J.; Vernevaut, M.F.; Siess, M.H. *Xenobiotica,* **1996**, *26,* 49.
[44] Breinholt, V.; Lauridsen, S.T.; Daneshvar, B.; Jakobsen, J. *Cancer Lett.,* **2000**, *154,* 201.
[45] Wang, W.; Higuchi, C.M. *Cancer Lett.,* **1995**, *98,* 63.
[46] Ben-Dor, A.; Steiner, M.; Gheber, L.; Danilenko, M.; Dubi, N.; Linnewiel, K.; Zick, A.; Sharoni. Y.; Levy, J. *Mol. Cancer Ther.,* **2005**, *4,* 177.
[47] Karas, M.; Amir, H.; Fishman, D.; Danilenko, M.; Segal, S.; Nahum, A.; Koifmann, A.; Giat, Y.; Levy, J.; Sharoni, Y. *Nutr. Cancer,* **2000**, *36,* 101.
[48] Nahum, A.; Hirsch, K.; Danilenko, M.; Watts, C.K.; Prall, O.W.; Levy, J.; Sharoni. Y. *Oncogene,* **2001**, *20,* 3428.
[49] Kotake-Nara, E.; Kushiro, M.; Zhang, H.; Sugawara, T.; Miyashita, K.; Nagao, A. *J. Nutr.,* **2001**, *131,* 3303.
[50] Kotake-Nara, E.; Asai, A.; Nagao, A. *Cancer Lett*., **2005**, *220*, 75.
[51] Pasquali, D.; Rossi, V.; Bellastella, G.; Bellastella, A.; Sinisi, A.A. *Curr. Pharm. Des.,* **2006**, *12,* 1923.
[52] Aboseif, S.R.; Dahiya, R.; Narayan, P.; Cunha, G.R. *Prostate,* **1997**, *31,* 161.
[53] Lohnes, D.; Kastner, P.; Dierich, A.; Mark, M.; LeMeur, M.; Chambon, P., *Cell,* **1993,** 7*3***,** 643.
[54] Blutt, S.E.; Allegretto, E.A.; Pike, J.W.; Weigel, N.L. *Endocrinology,* **1997**, *138,* 1491.
[55] Pasquali, D.; Rossi, V.; Prezioso, D.; Gentile, V.; Colantuoni, V.; Lotti, T.; Bellastella, A.; Sinisi, A.A. *J. Clin. Endocrinol. Metab.,* **1999**, 8*4,* 1463.
[56] Young**,** C.Y.; Murtha, P.E.; Andrews, P.E.; Lindzey, J.K.; Tindall, D.J. *Prostate,* **1994**, *25,* 39.
[57] Tokumaru, Y.; Harden, S.V.; Sun, D.I.; Yamashita, K.; Epstein, J.I.; Sidransky, D. *Clin. Cancer Res.,* **2004**, *10,* 5518.
[58] Lotan, R.; Lotan, Y. *Clin. Cancer Res.,* **2004**, *10,* 3935; Khachik, F. *Pure Appl. Chem.,* **2006**, *78,* 1551.
[59] Fang, M.Z.; Chen, D.; Sun, Y.; Jin, Z.; Christman, J.K.; Yang, C.S. *Clin. Cancer Res.,* **2005**. *11,* 7033.
[60] Qian DZ, Ren M, Wei Y, Wang X, van de Geijn F, Rasmussen C, Nakanishi O, Sacchi N, Pili R. *Prostate,* **2005**, *64,* 20.
[61] Mehta, P.P.; Bertram, J.S.; Loewenstein, W.R *J. Cell Biol.,* **1989**, *108***,** 1053.
[62] Mitra, S.; Annamalai, L.; Chakraborty, S.; Johnson, K.; Song, X.H.; Batra, S.K.; Mehta, P.P. *Mol. Biol. Cell,* **2006**, *17,* 5400.
[63] Oyamada, M.; Oyamada, Y.; Takamatsu, T. *Biochim. Biophys. Acta,* **2005**, *1719,* 6.
[64] Zhang, L.-X.; Cooney, R.V.; Bertram, J.S. *Carcinogenesis,* **1991**, *12***,** 2109.
[65] McLachlan, E.; Shao, Q.; Wang, H.L.; Langlois, S.; Laird, D.W. *Cancer Res.,* **2006**, *66,* 9886.
[66] Yamasaki, H. *Carcinogenesis,* **1990**, *11,* 1051.
[67] Vine, A.L.; Bertram, J.S. *Nutr. Cancer,* **2005**, *52,* 105.
[68] Vine, A.L.; Bertram, J.S.; Vine, A.L.; Leung, Y.M.; Bertram, J.S. *Mol. Carcinog.,* **2005**, *43,* 75.
[69] Kucuk, O.; Sarkar, F.H.; Sakr, W.; Djuric, Z.; Pollak, M.N.; Khachik, F.; Li, Y.W.; Banerjee, M.; Grignon, D. Bertram, J.S.; Crissman, D.; Pontes, E.J.; Wood, D.P. Jr., *Cancer Epidemiol. Biomark. Prev.,* **2001**, *10***,** 861.
[70] Ansari, M.S.; Gupta, N.P. *BJU Int.,* **2003**, *92,* 375.
[71] Kim, H.S.; Bowen, P.; Chen, L.; Duncan, C.; Ghosh, L.; Sharifi, R.; Christov, K. *Nutr. Cancer,* **2003**, *47,* 40.
[72] Ablin, R.J. *Am. J. Health Syst. Pharm.,* **2005**, *62,* 899.
[73] Forbes, K.; Gillette, K.; Sehgal, I. *Exp. Biol. Med. (Maywood),* **2003**, *228,* 967.
[74] Mills, P.K.; Beeson, W.L.; Phillips, R.L.; Fraser, G.E. *Cancer,* **1989**, *64***,** 598.
[75] Giovannucci, E.; Ascherio, A.; Rimm, E.B.; Stampfer, M.J.; Colditz, G.; Willett, W.S. *J. Natl. Cancer Inst.,* **1995**, *87*, 1767.
[76] Giovannucci, E.; Rimm, E.B.; Liu, Y.; Stampfer, M.J.; Willett, W.C. *J. Natl. Cancer Inst.,* **2002**, *94,* 391.
[77] Wu, K.N.; Erdman, J.W.; Schwartz, S.J.; Platz, E.A.; Leitzmann, M.; Clinton, S.K.; DeGroff, V.; Willett, W.C.; Giovannuci, E. *Cancer Epidemiol. Biomark. Prev.,* **2004**, *13,*260.
[78] Cook, N.R.; Stampfer, M.J.; Ma, J.; Manson, J.E.; Sacks, F.M.; Buring, J.E.; Hennekens, C.H. *Cancer,* **1999**, *86***,** 1783.
[79] Heinonen, O.P.; Albanes, D.; Virtamo, J.; Taylor, P.R.; Huttunen, J.K.; Hartman, A.M.; Haapakoski, J.; Malila, N.; Rautalahti, M.; Ripatti, S.; Maenpaa, H.; Teerenhovi, L.; Koss, L.; Virolainen M.; Edwards**.,** B.K. *J. Natl. Cancer Inst.,* **1998**, *90***,** 440.
[80] Omenn, G.S.; Goodman, G.E.; Thornquist, M.D.; Balmes, J.; Cullen, M.R.; Glass, A.; Keogh, J.P.; Meyskens, F.L. Jr.; Valanis, B.; Williams, J.H. Jr.; Barnhart, S.; Cherniack, M.G.; Brodkin, C.A.; Hammar, S. *J. Natl. Cancer Inst.,* **1996**, *88***,** 1550.
[81] Omenn, G.S.; Goodman, G.E.; Thornquist, M.D.; Balmes, J.; Cullen, M.R.; Glass, A.; Keogh, J.P.; Meyskens, F.L.; Valanis, B.; Williams, J.H.; Barnhart, S.; Hammar, S. *N. Engl. J. Med.,* **1996**, *334,* 1150.
[82] Nomura AM, Stemmermann GN, Lee J, Craft NE. *Cancer Epidemiol. Biomark. Prev.,* **1997**, 6, 487.

[83] Chang, S.; Erdman, J.W. Jr.; Clinton, S.K.; Vadiveloo, M.; Strom, S.S.; Yamamura, Y.; Duphorne, C.M.; Spitz, M.R.; Amos, C.I.; Contois, J.H.; Gu, X.; Babaian, R.J.; Scardino, P.T.; Hursting, S.D. *Nutr. Cancer,* **2005**, *53,* 127.

[84] Kirsh, V.A.; Hayes, R.B.; Mayne, S.T.; Chatterjee, N.; Subar, A.F.; Dixon, L.B.; Albanes, D.; Andriole, G.L.; Urban, D.A.; Peters, U.A. *Cancer Epidemiol. Biomark. Prev.,* **2006**, *15,* 92.

[85] Kirsh, V.A.; Hayes, R.B.; Mayne, S.T.; Chatterjee, N.; Subar, A.F.; Dixon, L.B.; Albanes, D.; Andriole, G.L.; Urban, D.A.; Peters, U. *J. Natl. Cancer Inst.,* **2006**, *98,* 245.

[86] Peters, U.; Leitzmann, M.F.; Chatterjee, N.; Wang, Y.; Albanes, D.; Gelmann, E.P.; Friesen, M.D.; Riboli, E.; Hayes, R.B. *Cancer Epidemiol. Biomark. Prev.,* **2007**, 16, 962.

[87] McCann, S.E.; Ambrosone, C.B.; Moysich, K.B.; Brasure, J.; Marshall, J.R.; Freudenheim, J.L.; Wilkinson, G.S.; Graham, S. *Nutr. Cancer,* **2006**, *53,* 33.

[88] Kristal, A.R. *J. Urol.,* **2004**, *171,* S54.

[89] Albanes, D.; Heinonen, O.P.; Taylor, P.R.; Virtamo, J.; Edwards, B.K.; Rautalahti, M.; Hartman, A.M.; Palmgren, J.; Freedman, L.S.; Haapakoski, J.; Barrett, M.J.; Pietinen, P.; Malila, N.; Tala, E.; Liippo, K.; Salomaa, E.R.; Tangrea, J.A.; Teppo, L.; Askin, F.B.; Taskinen, E.; Erozan, Y.; Greenwald, P.; Huttunen, J.K. *J. Natl. Cancer Inst.,* **1996**, *88,* 1560.

[90] Mayne, S.T.; Lippman, S.M. *J. Natl. Cancer Inst.,* **2005**, *97,* 1319.

[91] Baron, J.A.; Cole, B.F.; Mott, L.; Haile, R.; Grau, M.; Church, T.R.; Beck, G.J.; Greenberg, E.R. *J. Natl. Cancer Inst.,* **2003**, *95,* 717.

[92] Greenberg, E.R.; Baron, J.A.; Stukel, T.A.; Stevens, M.M.; Mandel, J.S.; Spencer, S.K. *N. Engl. J. Med.,* **1990**, *323,*789.

[93] Touvier, M.; Kesse, E.; Clavel-Chapelon, F.; Boutron-Ruault, M.C. *J. Natl. Cancer Inst.,* **2005**, *97,* 1338.

[94] Keijer, J.; Bunschoten, A.; Palou, A.; Franssen-van Hal, N.L. *Biochim. Biophys. Acta,* **2005**, *1740,* 139.

[95] Liu, C.; Wang, X.D.; Bronson, R.T.; Smith, D.E.; Krinsky, N.I.; Russell, R.M. *Carcinogenesis,* **2000**, *21,* 2245.

[96] Paolini, M.; Cantelli-Forti, G.; Perocco, P.; Pedulli, G.F.; Abdel-Rahman, S.Z.; Legator, M.S. *Nature,* **1999**, *398,* 760.

[97] Perocco, P.; Paolini, M.; Mazzullo, M.; Biagi, G.L.; Cantelli-Forti, G. *Mutat. Res.,* **1999**, *440,* 83.

[98] Wang, X.D.; Liu, C.; Bronson, R.T.; Smith, D.E.; Krinsky, N.I.; Russell, M. *J. Natl. Cancer Inst.,* **1999**, *91,* 60.

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