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DOES BETA-CAROTENE PREVENT CANCER? A CRITICAL APPRAISAL

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ABSTRACT

The possible role of beta-carotene as a protective nutrient against cancer is reviewed. Human prospective and retrospective studies strongly indicate that beta-carotene protects against lung cancer and probably against stomach cancer. It may also be protective against cancer of the ovary, cervix, breast and other cancers, but not the colon or rectum. The protective factor appears to be beta-carotene itself, rather than total vitamin A. Experiments using a variety of animal models also show that beta-carotene is anti-carcinogenic and appears to act at several stages of the process. Possible mechanisms of action are discussed, namely that it must first be converted to vitamin A, that it alters carcinogen metabolism, that it is an anti-oxidant and that it enhances the immune defenses.

Key Words: beta-carotene, carotene, vitamin A, cancer

INTRODUCTION

In 1981, Peto et al. (1) reinterpreted various data and hypothesized that beta-carotene had a specific preventive action against cancer. This sparked much active interest and numerous reports have now appeared to shine much new light on the question. The hypothesis resembles Burkitt's concept of dietary fiber in that what started with the great virtue of simplicity has proved, on more careful scrutiny, to be considerably more complex (2).

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The major part of the evidence of the preventive effect of beta-carotene has come from studies on humans with and without cancer. Such evidence, more often than not, presents serious problems of interpretation (3). Frequently, the parameter measured is dietary total vitamin A (ie. retinol plus beta-carotene). However, retinol and its analogues also have anti-carcinogenic properties (4-6). Even where beta-carotene has been specifically measured, it is also strongly associated with the consumption of green and yellow vegetables. Thus the true protective factor might be beta-carotene, dietary fiber indoles, phenols, glucuronidase inhibitors, or even a low intake of meat. On top of these problems dietary assessment has an inherent lack of precision. Furthermore, if dietary assessment done on patients who already have cancer (retrospective studies), then the disease may have affected the diet (or the subject's memory of his diet).

Often beta-carotene status has been quantitated on the basis of blood analysis. Unlike blood retinol, the blood level of beta-carotene is a reliable index of dietary intake (7,8). Even so, in the context of cancer studies it may merely be an indirect measure of other dietary components.

Another problem is the matching of cases and controls. Ideally, an array of possibly relevant factors should be considered, either in the matching itself, or subsequently by analyzing the results using multiple regression. Smoking is particularly important. Apart from its close association with several types of cancer, smokers have a below average dietary intake (9) and blood level (10-14) of carotene.

LUNG CANCER

Dietary or blood indicators of beta-carotene intake are closely related to lung cancer risk (Table 1). The evidence strongly suggests that persons with a low intake of beta-carotene are at a 30 to 220% higher risk than otherwise similar people whose intake is relatively high (9,12,13,15-23).

Several of the studies provided data on the different histological types of lung cancer. Beta-carotene is most protective with squamous cell and small cell carcinoma but is generally not protective against adenocarcinoma (15,19,22-24).

The question arises as to what is the true protective factor. The only two plausible candidates are beta-carotene itself and total vitamin A. Good evidence points to the former. First, blood retinol levels have little or no relationship with lung cancer (13,15,25,26). Menkes et al. (15) pointed out that only studies using small numbers of subjects have reported a relationship with lung cancer risk and vitamin A. Similarly, where dietary carotene and retinol have been simultaneously measured, it is the former

TABLE 1

Relationship Between Measures of Beta-carotene Status and Risk of Lung Cancer

Measurement	No. of cancers and sex	No. of controls	Type of study*	Relative risk or case-control difference†	Place	Reference
serum beta-carotene	99 M/F	196	P	2.2, 1.7, 1.8, 1.2, 1.0 (p = 0.04)	Maryland	15
plasma beta-carotene	35 M	102#	P	38% lower (P = 0.0006)	Basel	12
serum beta-carotene	74 M	302	P	2.2, 2.4, 1.2, 1.5, 1.0 (p = 0.04)	Hawaii	13
dietary total carotene	447 M/F	759	R	1.3, 1.2, 1.0 (NS)§	New Mexico	16
dietary total carotene	364 M/F	627	R	1.6, 1.2, 1.1, 1.0 (p < 0.05)**	Hawaii	17
dietary total vitamin A††	514 M	1238	R	1.4, 1.0, 1.0 (p < 0.05)	Roswell Park	18
dietary total vitamin A	104 M/F	16,713	P	1.9, 1.0 (p = 0.02)	Norway	19
dietary total vitamin A	100 M/F	173	R	overall, slightly lower##	London	20
yellow/green vegetables	611 M 196 F	122,261# 142,857#	P	1.3, 1.0 1.5, 1.0	Japan	21
dietary total carotene	33 M	1954	P	7.0, 5.5, 3.0, 1.0 (p = 0.003)	Chicago	9
dietary total carotene	763 M	900	R	1.3, 1.3, 1.0 (p = 0.05)	New Jersey	22
dietary beta-carotene	216 F	216	R	2.5, 1.3, 0.8, 1.0 (p < 0.05)	Los Angeles	23

*Dietary data or blood samples were collected before (Prospective P) or after (Retrospective R) the development of the cancer.

†Relative risk is presented so that risk in group with highest intake or blood level is 1.0, case-control difference is intake or blood level in cases relative to controls.

#Controls not matched for smoking.

§NS, not significant, carotene was protective in Anglos who were ex-smokers rather than in hispanics or current smokers.

**Relationship seen in men but not women.

††Essentially an index of beta-carotene.

##Results inconsistent between sexes, cases had a much lower intake of vitamin A from supplements.

that shows the stronger relationship with lung cancer risk (9,16,22,23).

GASTROINTESTINAL CANCER

With the exception of one study (18), a low beta-carotene intake is frequently associated with stomach cancer (Table 2). Hirayama (28) reported from Japan that in areas where consumption of yellow and/or green vegetables is high, mortality rates for stomach cancer tend to be low ((r = -0.389, p < 0.05).

As with lung cancer the true protective factor is more likely to be beta-carotene than total vitamin A. Thus, Stehr (27) found a weaker relative risk for low total dietary vitamin A than for beta-carotene, while Nomura et al. (13) saw no relationship for serum retinol. However, the confounding role of retinol and of other factors, particularly vitamin C and smoking, requires further clarification.

There is no evidence that beta-carotene has a significant role in human colorectal cancer (Table 2). The detailed analysis carried out by Kune et al. (29) indicated that the increased risk associated with a reduced beta-carotene intake is an artifact arising from the close relationship between beta-carotene and vegetables.

Further, a retrospective study in Israel of gastro-intestinal cancer with 406 male and female cases, of whom 38% had stomach cancer and 58% colorectal cancer, were compared with 812 controls (31). No association was seen with dietary carotene.

FEMALE REPRODUCTIVE CANCERS

Ovarian cancer appears to be associated with a low intake of beta-carotene, but only in younger women (Table 3). Beta-carotene also seems protective against breast cancer, particularly in post-menopausal women (Table 3). Neither the ovarian cancer study (32) nor the Guernsey study (34) saw a relationship for retinol status thus indicating that in each cancer beta-carotene specifically is the protective factor.

With cervical cancer, the picture is unclear. Whereas the Roswell Park (18) and Atlanta studies (35) saw no relationship for dietary total vitamin A, the Bronx (36) and Milan (37) studies report that dietary beta-carotene had a strong inverse relationship with risk. The Milan study is probably the most reliable report due to its size, its focus on beta-carotene, and its allowance for the numerous confounding variables. It also showed an absence of a relationship for dietary retinol. Thus, a low beta-carotene intake is probably a risk factor, but this requires further investigation.

TABLE 2

Relationship Between Measures of Beta-carotene Status and Risk of Gastrointestinal Cancer*

Cancer	Measurement	No. of cancers and sex	No. of controls	Type of study	Relative risk or case-control difference	Place	Reference
stomach	dietary total vitamin A†	179 M 83 F	1238 1680	R	0.9, 0.6, 1.0 (NS) 0.8, 0.8, 1.0 (NS)	Roswell Park	18
stomach	dietary beta-carotene	111 M/F	not stated	R	2.0, 1.0	Pennsylvania	27
stomach	yellow/green vegetables	3913 M/F	265,118	P	1.3, 1.1, 1.0 ($p < 0.00015$)	Japan	28
stomach	serum beta-carotene	70 M	302	P	21% lower (NS)	Hawaii	13
stomach	plasma beta-carotene	19 M	37	P	33% lower (NS)	Basel	12
colorectal	plasma beta-carotene	14 M	33	P	21% lower (NS)	Basel	12
colorectal	serum beta-carotene	113 M	302	P	15% lower (NS)	Hawaii	13
colon rectum	dietary total vitamin A†	219 M 300 M	1238	R	1.0, 1.0, 1.0 1.1, 0.9, 1.0	Roswell Park	18
colon rectum		241 F 217 F	1680		0.8, 0.8, 1.0 1.3, 1.3, 1.0 (NS)		
colorectal	dietary beta-carotene	388 M 327 F	398 329	R	6% lower (M) or 11% lower (F) ($p < 0.01$ in each sex)	Melbourne	29
colorectal	dietary beta-carotene	245 M 174 F	489 345	R	1.2, 0.9, 0.8, 0.8, 1.0 (NS) 0.6, 0.5, 0.6, 0.6, 1.0 (NS)	Adelaide	30
colorectal	dietary total carotene	49 M	1954	P	7% higher (NS)	Chicago	9

*Details as Table 1. In some cases data on colon and rectal cases have been merged.

†Essentially beta-carotene.

TABLE 3

Relationship Between Measures of Beta-carotene Status and Risk of Female Reproductive Cancers*

Cancer	Measurement	No. of cancers and sex	No. of controls	Type of study	Relative risk or case-control difference	Place	Reference
ovary	dietary beta-carotene	93†	383	R	2.3, 1.4, 1.0 ($p<0.01$)#	Roswell Park	32
breast	dietary total vitamin A§	1025**	475	R	1.5, 1.4, 1.4, 1.0 ($p<0.05$)††	Roswell Park	33
breast	plasma beta-carotene	39##	78	P	2.8, 1.9, 2.4, 2.1, 1.0 (NS)	Guernsey Isles	34
uterus	dietary total vitamin A§	422	1680	R	1.2, 1.1, 1.0 (NS)	Roswell Park	18
cervix	dietary total vitamin A§	947	1680	R	1.1, 1.0, 1.0 (NS)	Roswell Park	18
intra-epithelial neoplasia of cervix	dietary total vitamin A	50	50	R	5% higher (NS)	Atlanta	35
severe dysplasia or carcinoma in situ of cervix	dietary beta-carotene	25	82	R	3.1, 1.0 ($p < 0.01$)	Bronx, NY	36
invasive cervical cancer	dietary beta-carotene	191	191	R	6.6, 3.0, 1.0 ($p < 0.001$)	Milan	37

*Details as Table 1.
†Subjects are age 30-49.
#After multiple regression the relative risk is reduced but is still significant ($p < 0.05$), protection not seen at age 50-79 (181 cases vs 651 controls).
§Essentially beta-carotene.
**subjects are age 55 or over.
††Protection not seen at age under 55 (999 cases vs 988 controls).
##Subjects are half pre- and half post-menopausal.

OTHER CANCERS

Prostate cancer presents an inconsistent picture (Table 4). Thus there are two studies in the U.S. which have indicated that a high intake of vitamin A may actually be a risk factor (38,39) whereas another study in Japan suggests that yellow and/or green vegetables are protective (21).

There is limited evidence that beta-carotene may be protective against cancer of the larynx, tongue, esophagus and bladder (Table 5) but in each case the confounding effects of other factors such as retinol and vitamin C needs elucidating (13,18,40-42).

EXPERIMENTAL TUMORS

Beta-carotene has demonstrated a preventive action against a variety of tumor types (Table 5). We (45) recently showed that in mice treated with 1,2-dimethylhydrazine (DMH) beta-carotene causes a fall in tumor incidence by about half (96% for adenocarcinomas, 40% for adenomas). Tumor multiplicity was similarly reduced. Mouse mortality, measured from the time when tumors were already present, also fell by about half. The dose of beta-carotene (20 mg/kg diet) is equivalent to about 150 to 300 g carrots per 3000 kcals, and is therefore in the nutritionally relevant range. It is the lowest dose yet shown to be anti-carcinogenic. However, a similar experiment on rats showed no reduction in the yield of tumors in the colon and small intestine (46). There are several differences between this experiment and ours, which might account for these contradictory findings. The rat study used a 500 times higher dose of beta-carotene, the species difference, and their control group had a tumor incidence of 100% (versus 74% in our study).

Several studies (47-50) have provided firm evidence that beta-carotene prevents skin tumors (Table 5). In each case the dose level of beta-carotene used was many times greater than can be obtained from natural foods. It is unclear how much of this protection is specific to the carcinogenic action of UV light. These experiments hold much promise if beta-carotene or, perhaps, other carotenoides will prevent skin cancer in high risk individuals, such as fair skinned people frequently exposed to bright sunshine.

MECHANISM OF ACTION

An important question is whether beta-carotene is most effective at the initiation or promotion stage of carcinogenesis.

TABLE 4

Relationship Between Measures of Beta-carotene Status and risk of Various Cancers*

Cancer	Measurement	No. of cancers and sex	No. of controls	Type of study	Relative risk or case-control difference	Place	Reference
prostate	dietary total vitamin A†	311 M	294	R	0.6, 0.8, 1.3, 1.0 ($p<0.01$)#	Roswell Park	38
prostate	dietary total vitamin A	181 M	181	R	higher by 20% (age 30-49; $p < 0.007$) or by 13% (age 50 and over; $p < 0.069$)	Washington	39
prostate	green/yellow vegetables	63 M	122,261	P	2.5, 1.6, 1.0	Japan	21
leukemia	dietary total vitamin A†	130 M 61 F	1238 1680	R	0.5, 0.7, 1.0 ($p = 0.01$) 0.8, 1.1, 1.0 (NS)	Roswell Park	18
larynx	dietary total vitamin A†	338 M	359	R	3.0, 1.9, 2.1, 1.0 ($p<0.005$)	Roswell Park	40
tongue	dietary total vitamin A†	173 M	1238	R	1.7, 1.3, 1.0 ($p < 0.01$)	Roswell Park	18
esophagus	dietary total vitamin A†	147 M	264	R	1.9, 1.6, 1.0 ($p = 0.033$)	Roswell Park	41
bladder	dietary total vitamin A†	489 M/F	901	R	2.1, 1.9, 1.7, 1.2, 1.4, 1.2, 1.0 ($p < 0.01$)	Roswell Park	42
bladder	serum beta-carotene	27 M	302	P	same in cases and controls	Hawaii	13
various	green/yellow vegetables	42 M/F§	904	P	3.3, 2.7, 3.0, 1.3, 1.0 ($p < 0.01$)	Massachusetts	43
various	serum total carotene	111 M/F**	210	P	0.7, 1.1, 1.1, 1.1,1.0 (NS)††	various places in U.S.A.	44

*Details as Table 1.
†Essentially beta-carotene.
#Risk was stronger at age 70 and over than at age under 70.
§Cancer cases: breast 6, lung 10, intestine 4, other 22.
**Cancer cases: breast 14, lung 17, gastrointestinal 11, prostate 11, leukemia and lymphoma 11, other 40.
††Over half of this relative risk for a raised serum carotene level comes from leukemia and lymphoma.

TABLE 5

Effect of Beta-Carotene on Experimental Carcinogenesis

Species	Cancer Inducing Agent	Tumor	Beta-Carotene (mg/kg diet)	Effect	Reference
Mouse	DMH	colon	20	tumor yield and mortality reduced	45
Rat	DMH	colon and small intestine	10,000	no effect	46
Mouse	DMBA*/UV/croton oil	skin	33,000	delayed tumor appearance reduced tumor yield†	47
Mouse	DMBA/croton oil	skin papilloma	200#	tumors regressed§	48
Mouse	BP+/UV	skin	**	reduced tumor incidence††	49
Mouse	UV	skin (squamous cell carcinoma)	##	delayed tumor appearance reduced tumor growth rate	50
Hamster	DMBA/benzoyl peroxide	Buccal pouch (epidermoid carcinoma)	(topical)	reduced tumor yield	51
Rat	DMBA	submandibular gland	5-250	delayed tumor appearance reduced tumor size & incidence§§	52
Rat	DMBA (ig)	not specified	90++	reduced tumor incidence and multiplicity	53
Rat	DMBA (ig)	not specified	45-270	reduced tumor yield‡‡	54
Mouse	oncogenic virus	--	90-120	delayed tumor appearance reduced tumor incidence improved tumor regression	55
Mouse	transplated adenocarcinoma cells	--	90	delayed tumor appearance decreased tumor incidence increased survival time	56

*DMBA, 7,12-dimethylbenz(a)anthracene.
†Protection seen both with and without UV.
#Beta-carotene not given until tumors already present.
§Only 5 mice in each of the 2 groups.
+BP, benzo(a)pyrene
**500 mg/kg diet plus 100 mg/kg body wt ig.
††Tumor incidence reduced approximately 50% in group given BP and UV but only a slight reduction in group given BP alone.
##5-25 mg per mouse thrice weekly by ip injection.
§§25-250 mg/kg doses were of similar effectiveness but 5 mg/kg was ineffective.
++Beta-carotene given only after carcinogen.
‡‡Beta-carotene supplementation stopped one day before carcinogen administration, all doses of beta-carotene gave a similar response.

The best evidence comes from a hamster study which showed beta-carotene to be clearly effective at both stages (51). Similarly, beta-carotene was shown to inhibit DMBA induced transformation of mouse mammary cells in vitro, with activity apparently occurring at both stages (57). Other studies listed in Table 5 have indicated that beta-carotene can be effective when given before the carcinogen (54), after the carcinogen (53) or else after tumors are already present (48). The experiments using an oncogenic virus (55) and a transplantable tumor (56) point to a late stage effect. In our mouse colon study beta-carotene did not affect DMH induced colon mucosal hyperplasia, suggesting that the protective effect occurred during promotion (45). In summary, beta-carotene appears to block the initiation, promotion and subsequent development of tumors.

There are several possible mechanisms to account for the anti-carcinogenicity of beta-carotene. It may require prior conversion to retinol. However, this is a doubtful mode of action in either humans or experimental animals. As noted earlier, studies on human lung cancer strongly indicate that the protective action of beta-carotene is not shared by retinol (9,12,13,15-23). Weaker evidence suggests that this is also the case in stomach and cervical cancer (12,13,18,27,28,35-37). Further experiments on rats using retinol or retinoids have seen only a much weaker protective effect (58-61). Similarly, the preventive action of beta-carotene against DMBA induced submandibular gland tumors of rats (Table 5) is not shared by 13-cis-retinoic acid (62). The study reporting that beta-carotene prevented DMBA induced in vitro transformation of mouse mammary cells also observed that there was no accumulation of retinol (57), and thus beta-carotene itself seems to be the active compound.

If the anti-carcinogenic action of beta-carotene does not depend on retinol formation, then carotenoids which lack pro-vitamin A activity should also be anti-carcinogenic. Canthaxanthin is such a carotenoid and does indeed protect mice against skin tumor formation (47,49). However, this may merely reflect a specific protective effect against UV light. In a trial on Philipino betel nut and tobacco chewers, beta-carotene, but not canthaxanthin, protected against chromosome breakage in the oral mucosal cells (63). Conceivably, beta-carotene has a specific anti-carcinogenic action which is independent of its vitamin A activity, and this action is not shared by other carotenoids. Alternately, the anti-carcinogenicity of beta-carotene may reflect its vitamin A activity but only in specific tissues.

We (64) recently observed that dietary beta-carotene alters the hepatic levels of certain drug metabolizing enzymes. When mice received supplemental beta-carotene (20-500 mg/kg diet), there was a marked decrease in the activity of both cytochrome P-450 and biphenyl 4-hydroxlyase, though not in antipyrine N-demethylase or p-nitroanisole O-demethylase. Possibly this might cause carcinogens to be shunted along a detoxification rather than an activation pathway. This, of course, presupposes that

beta-carotene is active during the initiation stage of carcinogenesis.

It has been suggested that beta-carotene may have an anti-oxidant property, especially at the relatively low oxygen partial pressures found in most tissues under physiological conditions (65,77). The presumed mechanism is by trapping free radicals. We investigated this by measuring two liver indices of tissue oxidation, namely superoxide dismutase and malonaldehyde. However, neither was altered by supplemental beta-carotene (64). Similarly, the liver and plasma level of malonaldehyde in rats is not altered by dietary beta-carotene (although, significantly, it is increased by dietary 13-cis-retinoic acid) (66). On the other hand beta-carotene protects guinea-pigs against chloroform induced lipid peroxidation (67).

Another possible mechanism of action of beta-carotene is by enhancement of the immune defense (68). This concept is supported by the fact that beta-carotene achieves at least part of its protective effect in late carcinogenesis. The nutrient enhances the immune response of rat colorectal tissue (69), increases the cytotoxicity of macrophages towards hamster tumor cells (70) and enhances thymic function, particularly lymphocyte production (55). Beta-carotene also influences human interferon action, an effect opposite in direction to that of retinoic acid (71,72).

COMMENT

The ideal strategy in the war on cancer is to learn how to prevent it as well as cure it. In this regard beta-carotene is well on its way to being an important weapon. It appears to help prevent several cancers, particulary of the lung. That it apparently achieves much of its effectiveness in late carcinogenesis is particularly valuable. There is ample justification to recommend that the general population emphasizes green and yellow vegetables. Quite apart from beta-carotene, they also have many nutritional virtues.

While it is possible that beta-carotene supplementation may have potential value to high-risk individuals, there is still much to be learned before recommendation can be made for the carotenoid supplementation to prevent cancer. Animal experiments need to be extended to cover more organ systems (very little has been done on animal models of major human cancers). We need to know the relative effectiveness of nutritional and pharmacological dosages of beta-carotene, as well as the stage at which they work (different dosages may work at different stages). Further immunological work should prove profitable.

Human studies, both diet and blood, have looked at either beta-carotene specifically, or at total carotene. Blood beta-carotene is only 16% of total carotene (73). What is the

importance of carotenes other than beta-carotene? There is still a great need for human studies on the relationship between carotenoids and cancer risk. We would urge anyone contemplating such an investigation to study the papers by Peto et al. (1), Peto (74) and Palgi (3). Two primary prevention trials employing beta-carotene supplements are currently in progress, one with physicians in the U.S.A. (75) and another on smokers in Finland (76). Hopefully, the results will prove to be highly rewarding.

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