Meeting Report

An International Evaluation of the Cancer Preventive Potential of Vitamin A[1]

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Abstract

The IARC convened a Working Group of experts in May 1998 to evaluate the cancer preventive potential of vitamin A and to compile the third volume of the *IARC Handbooks of Cancer Prevention*. The handbook is intended to provide a comprehensive review of the relevant information in the published scientific literature through April 1998 on the role of vitamin A in cancer prevention. The focus of this critical review and commentary is on retinol and the retinyl esters. Much of the scientific literature in this field overlaps with studies involving vitamin A metabolites, vitamin A precursors, and studies of total dietary vitamin A (which is a combination of preformed vitamin A and its precursors), so work from this wide range of research is included in this review when it is deemed relevant to our understanding of the effects of retinol or retinyl esters on cancer development. The observed effects of preformed vitamin A on cell and organ culture, on animal models, in dietary observational epidemiological studies, and in human intervention studies was reviewed in the meeting. In summary, there is little evidence that vitamin A intake has any substantial cancer-preventive effects.

Introduction

In 1926, Fujimaki called attention to a possible relationship between vitamin A deficiency and carcinogenesis. In the next 2 decades, retinol deficiency was found to inhibit the differentiation of mesenchymal cells to vascular cells in chick embryo (1). Subsequently, the roles of retinoic acid and its 9-*cis* isomer were established in controlling cell differentiation, growth, and reproduction (2–4). In the past 20 years, vitamin A has been extensively studied as a cancer chemopreventive agent. Several reviews of chemoprevention studies using vitamin A in cell culture, in animals, and in man have been published in recent years (5–14).

Vitamin A deficiency is clearly a continuing public health problem in many areas of the world (15). Because vitamin A deficiency can lead to an increased risk for many health problems including infections and blindness, programs to supplement and fortify foods for undernourished populations continue to be an important public health priority. Patterns of cancer mortality worldwide do not correspond strongly to patterns of vitamin A deficiency except, perhaps, for cancers of the liver and stomach, sites that are thought to be etiologically related to both infectious and nutritional factors. The public health problem of vitamin A deficiency and the potential role of vitamin A in cancer prevention are, therefore, two important but distinctly different issues.

In much of the nutritional scientific literature, "vitamin A" is used as a generic term that refers to both preformed vitamin A (largely all-*trans*-retinol and its esters) and to some of the carotenoids. The third *IARC Handbook of Cancer Prevention* is focused on the cancer-preventive effects of the preformed vitamin A compounds, principally retinol and retinyl esters. Volume 2 in the IARC handbook series reviewed the carotenoids (16), and the forthcoming volume 4 will review in more detail retinoic acid, other retinoid metabolites, and synthetic retinoids.

Issues in Research on Vitamin A and Cancer

It is clear that an important limitation of the use of preformed vitamin A in cancer prevention in humans is the toxicity that is seen at high doses. Toxicities are seen in various organs, including the skin, circulation (*e.g.*, hypertriglyceridemia), liver, nervous system, and bones. Of particular concern regarding the widespread use of preformed vitamin A is the apparent sensitivity of the developing embryo to teratogenesis at levels of supplemental retinyl palmitate as low as 25,000 IU/day. This toxicity of preformed vitamin A has prompted the development of literally thousands of synthetic retinoids designed to have more specific beneficial properties, but with lower toxicity potential. An active retinoid without teratogenic potential is yet to be identified, however.

One of the particular challenges in interpreting studies of vitamin A effects on cancer is that studies have been done at widely differing levels of vitamin A nutritive status. For instance, several studies have indicated greater effects with supplementation in animals that were first fed vitamin A-deficient diets than among animals on normal diets. Such experimental studies involving humans who are maintained in a vitamin A-deficient state are obviously not ethically possible to conduct. Animal studies can also test the effects of vitamin A at high doses, where toxicities are often seen, whereas this type of research in human populations is also not possible.

A striking feature of vitamin A physiology is the strong mechanism of homeostatic control of the circulating concentrations of retinol across a broad range of intake of preformed vitamin A and pro-vitamin A. Therefore, much of the human observational and experimental work, which has been carried out within this homeostatically controlled range, may not be comparable with much of the animal experimental studies done at levels of deprivation or excess. Also related to the phenomenon of homeostasis is the limitation of the use of serum retinol

Received 6/22/98; revised 10/8/98; accepted 10/13/98.

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[1] Supported in part by the Foundation for Promotion of Cancer Research, Japan.

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Table 1 Reviewed studies on the intake of preformed vitamin A and risk of selected cancers

Site	Study type	Relative risk[a]		
		<1	1	>1
Lung	Case-control	2	10	1
	Cohort	1	3	1
	Trial	0	0	1[b]
Upper aero-digestive	Case-control	1	10	6
	Cohort	0	1	0
	Trial	0	2[c, d]	0
Gastric	Case-control	0	7	2
	Cohort	0	0	0
	Trial	0	2[c, d]	0
Colorectal	Case-control	1	7	0
	Cohort	0	4	0
	Trial	0	1[b, d]	0
Breast	Case-control	0	13	0
	Cohort	0	6	0
	Trial	0	1[b, d]	0
Prostate	Case-control	1	5	1
	Cohort	0	2	2
	Trial	0	1[b, d]	0
Bladder	Case-control	2	4	0
	Cohort	0	0	0
	Trial	0	1[b, d]	0

[a] Categories based on statistical significance ($P < 0.05$).
[b] Retinol combined with β-carotene.
[c] Retinol combined with zinc or multivitamins.
[d] Secondary end point in one study.

levels as a measure of vitamin A status. Circulating retinol concentrations remain fairly constant until liver reserves fall to very low levels, below 0.07 μmol/g (17), and factors other than intake (especially infection, malnutrition, and acute stress) can affect circulating retinol levels, thus limiting the utility of serum levels in other than long-term prospective studies. Vitamin A status can now be estimated by the relative dose response and the modified relative dose response tests that have been widely used to assess vitamin A deficiency states, but the more precise method of estimating total body stores, the isotope dilution methods with deuterated retinol (17), has not been widely used because it is technically demanding.

Observational studies have been based generally on estimates of preformed vitamin A in the diet, with some information from older studies that reported only total vitamin A, and a small number of studies related use of vitamin A supplements to cancer risk. Intervention studies have been conducted with vitamin A doses ranging from approximately 50–250% of typical total vitamin A dietary intakes. The period of supplementation has not extended beyond 5 years, and duration of follow-up has been limited.

Cancer-preventive Effects

No consistent association can be found between dietary intake of preformed vitamin A and risk of lung, gastric, colorectal, skin, breast, prostate, bladder, or cervical cancer in the reviewed observational studies (Table 1).

Intervention studies have shown no beneficial effect of retinol as compared with placebo on the incidence of basal-cell carcinoma. With respect to squamous cell carcinoma of the skin, a risk reduction was found in relatively moderate-risk individuals, but not in high-risk subjects (18, 19). No beneficial effect on gastric cancer was detected in two intervention studies in China, where retinol was given in addition to either zinc or a multivitamin preparation (20, 21). Data from a large randomized placebo-controlled trial among North American smokers and asbestos-exposed workers suggested, if anything, an adverse effect on lung cancer incidence of a combination of retinol with β-carotene (22). In one trial in treated lung cancer patients, supplementation with high-dose retinol was associated with a reduction in second primary lung cancers (23).

The risk of mesothelioma was reduced in an intervention trial among Australian asbestos miners given retinol as compared with those given β-carotene (24), but not affected by retinol in combination with β-carotene in a North American trial (22).

Case-control studies of oesophageal cancer suggested either a modest direct association with high dietary intake of retinol or no association. Two Chinese intervention trials did not show a beneficial effect on oesophageal cancer in which retinol was given in addition to zinc (20) or a multivitamin preparation (21).

Mechanisms of Cancer Prevention

Vitamin A may prevent or delay carcinogenesis at both the initiation and promotion steps. However, the mechanisms through which these effects may be exerted have not been fully elucidated. Although retinol can activate nuclear retinoid receptors via some of its metabolites, genes involved in chemopreventive actions that are indirectly regulated by retinol have not been identified. Plausible mechanisms based on findings in cultured cells and animal models include modulation of cell properties (cell proliferation, differentiation, communication, adhesion, migration, and invasion) or host properties (immune response, angiogenesis). Analysis of these mechanisms in the context of a chemoprevention trial is required for validation of their relevance.

Evaluation

There is evidence suggesting lack of cancer-preventive activity of preformed vitamin A for cancers at the following sites in humans: upper aerodigestive tract, lung, breast (among postmenopausal women), colorectal, bladder, prostate, and stomach. There is inadequate evidence with respect to possible cancer-preventive activity of preformed vitamin A at all other sites and for second primary cancers of the lung.

Observational studies and randomized controlled trials have been carried out within the broad range of intakes, which have little or no effect on the levels of retinol in the circulation (although they may well have influenced levels of more active metabolites or levels in other tissues). The results of these studies have been largely negative, supporting the conclusion that for most cancer sites the proponderance of evidence does not support a chemopreventive role for preformed vitamin A. The few randomized, controlled trials conducted to date likewise do not support the idea that preformed vitamin A has a substantial chemopreventive role for cancer. There is a suggestion of a possible benefit of preformed vitamin A against squamous cell skin cancer among those who have had previous skin cancers, against mesothelioma among asbestos-exposed workers, and against second primary lung cancers among those treated for lung cancer. However, the protective effects for skin cancer and mesothelioma have been seen in only one of the two published studies for each of these end points, and there has been only one study of preventing second primary cancers after lung cancer using very high doses of preformed vitamin A. It is important to note that all of the previous chemoprevention trials

of vitamin A in humans have been relatively short studies, none extending beyond 6 years. If vitamin A is protective at earlier stages of carcinogenesis, as is suggested by some *in vitro* studies showing that vitamin A can protect against genetic effects of certain carcinogens, longer treatment and longer follow-up would be needed to see preventive effects.

The benefits to health of correcting vitamin A deficiency are clear. Both animal experimental studies and human studies have shown that vitamin A deficiency enhances the severity of morbid conditions and increases total mortality. A limited number of animal studies also support the hypothesis that vitamin A deficiency increases cancer risk. Confirmatory studies in vitamin A-deficient populations are lacking. Two short-term cancer chemoprevention trials conducted among populations in China with multiple micronutrient insufficiency have shown no apparent effect of preformed vitamin A on cancer incidence.

The suggestion of potential chemopreventive benefits of high doses of preformed vitamin A in rat mammary cancer models are encouraging in that there may be similar benefits for humans, but the fact that these effects are typically seen only at doses that are toxic or teratogenic in humans limits enthusiasm for preformed vitamin A as a widely acceptable cancer chemopreventive agent. Therefore, research is now in progress to discover more effective and less toxic synthetic retinoids. This area of inquiry will be covered in volume 4 of this IARC handbook series.

In summary, there is little evidence to support the idea that within the wide range bordered by deficiency and toxicity modulating preformed vitamin A intake has any substantial cancer-preventive effect.

Acknowledgments

The Foundation for Promotion of Cancer Research Japan, is gratefully acknowledged for its generous support of the meeting of the Working Group and the production of the volume of the *IARC Handbooks of Cancer Prevention.*

Appendix

The meeting participants were W. S. Blaner (Columbia University, New York, NY), T. Byers, Chairman (University of Colorado, Denver, CO), J. A. Crowell (National Cancer Institute, Bethesda, MD), M. I. Dawson (SRI International, CA), S. De Flora (University of Genoa, Genoa, Italy), N. De Vries (Saint Lucas–Andreas Hospital, Amsterdam, the Netherlands), L. O. Dragsted (Institute of Food Safety and Toxicology, Soborg, Denmark), S. Franceschi (Aviano Cancer Center, PN, Italy), D. J. Hunter (Harvard School of Public Health and Channing Laboratory, Boston, MA), C. Ijsselmuiden, (University of Pretoria, Pretoria, South Africa), R. Lotan, (M. D. Anderson Cancer Center, Houston, TX), R. Mehta (University of Illinois, Chicago, IL), J. O. Moskaug (University of Oslo, Oslo, Norway), H. Nau (School of Veterinary Medicine, Hannover, Germany), P. Nettesheim (National Institute of Environmental Health Sciences, Research Triangle Park, NC), J. A. Olson (Iowa State University, Ames, IA), D. I. Thurnham, Vice-Chairman (University of Ulster, Londonderry, Northern Ireland), H. Tsuda (National Cancer Center Research Institute, Tokyo, Japan), A. Woodward (Wellington School of Medicine, Wellington South, New Zealand), R. A. Woutersen (TNO-Nutrition and Food Research Institute, Zeist, the Netherlands).

The meeting observer was U. Wiegand (Hoffmann-La Roche, Basel, Switzerland).

References

1. Sporn, M. B., and Roberts, A. B. Role of retinoids in differentiation and carcinogenesis. Cancer Res., *43:* 3034–3040, 1983.

2. Gudas, L. J., Sporn, M. B., and Roberts, A. B. Cellular biology and biochemistry of retinoids. *In:* M. B. Sporn, A. B. Roberts, and D. S. Goodman (eds.), The Retinoids. Biology, Chemistry, and Medicine, Ed. 2, pp. 443–519. New York: Raven Press, 1994.

3. Mangelsdorf, D. J., Umesono, K., and Evans, R. M. The retinoid receptors. *In:* M. B. Sporn, A. B. Roberts, and D. S. Goodman (eds.), The Retinoids. Biology, Chemistry, and Medicine, Ed. 2, pp. 319–349. New York: Raven Press, 1994.

4. Blomhoff, R. (ed). Vitamin A in Health and Disease, pp.1–677. New York: Marcel Dekker, 1994.

5. Kelloff, G. J., Boone, C. W., Malone, W. F., and Steele, V. E. Chemoprevention clinical trials. Mut. Res., *267:* 291–295, 1992.

6. Davison, A., Rousseau, E., and Dunn, B. Putative anticarcinogenic actions of carotenoids: nutritional implications. Can. J. Physiol. Pharmacol., *71:* 732–745, 1993.

7. Perera, F. P., Tang, D., Grinberg-Funes, R. A., Blackwood, M. A., Dickey, C., Blaner, W., and Santella, R. M. Molecular epidemiology of lung cancer and the modulation of markers of chronic carcinogen exposure by chemopreventive agents. J. Cell. Biochem., *17F:* 119–128, 1993.

8. Hong, W. K., and Itri, L. M. Retinoids and human cancer. *In:* M. B. Sporn, A. B. Roberts, and D. S. Goodman (eds.), The Retinoids. Biology, Chemistry, and Medicine, Ed. 2, pp. 597–629. New York: Raven Press, 1994.

9. Alberts, D. S., and Garcia, D. J. An overview of clinical cancer chemoprevention studies with emphasis on positive phase III studies. J. Nutr., *125:* 692S-697S, 1995.

10. Lippman, S. M., Heyman, R. A., Kurie, J. M., Benner, S. E., and Hong, W. K. Retinoids and chemoprevention: clinical and basic studies. J. Cell. Biochem. Suppl., *22:* 1–10, 1995.

11. Kelloff, G. J., Crowell, J. A., Hawk, E. T., Steele, V. E., Lubet, R. A., Boone, C. W., Covey, J. M., Doody, L. A., Omenn, G. S., Greenwald, P., Hong, W. K., Parkinson, D. R., Bagheri, D., Baxter, G. T., Blunden, M., Doeltz, M. K., Eisenhauser, K. M., Johnson, K., Knapp, G. G., Longfellow, D. G., Malone, W. F., Nayfield, S. G., Seifried, H. E., Swall, L. M., and Sigman, C. C. Strategy and planning for chemopreventive drug development: clinical development plans II. J. Cell. Biochem., *26S:* 54–71, 1996.

12. Khuri, F. R., Kurie, J. M., and Hong, W. K. Multidisciplinary care of lung cancer patients, Part II. Chemoprevention of respiratory tract cancer. Hematol. Oncol. Clin. N. Am. (U. S.), *11:* 387–408, 1997.

13. Minna, J. D., and Mangelsdorf, D. J. Retinoic acid receptor expression abnormalities in lung cancer: important clues or major obstacles? J. Natl. Cancer Inst., *89:* 602–604, 1997.

14. Sankaranarayanan, R., Mathew, B., Varghese, C., Sudhakaran, P. R., Menon, V., Jayadeep, A., Nair, M. K., Mathews, C., Mahalingam, T. R., Balaram, P., and Nair, P. P. Chemoprevention of oral leukoplakia with vitamin A and β carotene: an assessment. Oral Oncol., *33:* 231–236, 1997.

15. Sommer, A., and West, K. P., Jr. Vitamin A Deficiency: Health, Survival, and Vision, pp. 1–438. New York: Oxford Press, 1996.

16. IARC. Carotenoids. II. Handbooks of Cancer Prevention. Lyon, France: IARC, 1998.

17. Olson, J. A.Vitamin A, retinoids, and carotenoids. *In:* M. E. Shils, J. A. Olson, and M. Shike (eds.), Modern Nutrition in Health and Disease, Ed. 8, pp. 287–307. Philadelphia: Lea and Febiger, 1994.

18. Moon, T. E., Levine, N., Cartmel, B., Bangert, J. L., Rodney, S., Dong, Q., Peng, Y-M., and Alberts, D. S., for the Southwest Skin Cancer Prevention Study Group. Effect of retinol in preventing squamous cell skin cancer in moderate-risk subjects: a randomized, double-blind, controlled trial. Cancer Epidemiol. Biomark. Prev., *6:* 949–956, 1997.

19. Levine, N., Moon, T. E., Cartmel, B., Bangert, J. L., Rodney, S., Dong, Q., Peng, Y-M., and Alberts, D. S., for the Southwest Skin Cancer Prevention Study Group. Trial of retinol and isotretinoin in skin cancer prevention: a randomized, double-blind, controlled trial. Cancer Epidemiol. Biomark. Prev., *6:* 957–961, 1997.

20. Blot, W. J., Li, J-Y., Taylor, P. R., Guo, W., Dawsey, S., Wang, G-Q., Yang, C. S., Zheng, S-F., Gail, M., Li, G-Y., Yu, Y., Liu, B-Q., Tangrea, J., Sun, L-H., Liu, F., Fraumeni, J. F., Jr., Zhang, Y-H., and Bing, L. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combination, cancer incidence, and disease-specific mortality in the general population. J. Natl Cancer Inst., *85:* 1483–1492.

21. Li, J-Y., Li, J-Y., Taylor, P. R., Bing, L., Dawsey, S., Wang, G-Q., Ershow, A. G., Guo, W., Liu, Y., Yang, Shen, Q., Wang, W., Mark, S. D., Zou, X-N., Greenwald, P., Wu, Y-P., and Blot, W. J. Nutrition Intervention Trials in Linxian, China: multiple vitamin/mineral supplementation, cancer incidence, and disease-specific mortality among adults with esophageal dysplasia. J. Natl. Cancer Inst., *85:* 1492–1498, 1993.

22. 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., Jr, Barnhart, S., and Hammar, S. Effects of a combination of β carotene and vitamin A on lung cancer and cardiovascular disease. N. Engl. J. Med., *334:* 1150–1155, 1996.

23. Pastorino, U., Infante, M., Maioli, M., Chiesa, G., Buyse, M., Firket, P., Rosmentz, N., Clerici, M., Soresi, E., Valente, M., Belloni, P. A., and Ravasi, G. Adjuvant treatment of stage I lung cancer with high-dose vitamin A. J. Clin. Oncol., *11:* 1216–1222, 1993.

24. de Klerk, N. H., Musk, A. W., Ambrosini, G. L., Eccles, J. L., Hansen, J., Olsen, N., Watts, V. L., Lund, H. G., Pang, S. C., Beilby, J., and Hobbs, M. S. T. Vitamin A and cancer prevention II: comparison of the effects of retinol and β-carotene. Int. J. Cancer, *75:* 362–367.