10. Evaluation

10.1 Cancer-preventive activity

10.1.1 Humans

There is *evidence suggesting lack of cancer-preventive activity* of preformed vitamin A for cancers at the following sites: 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.

10.1.2 Experimental animals

There is *limited evidence* that retinyl esters have cancer-preventive activity in experimental animals. This evaluation is based upon consistent inhibitory effects in rat mammary cancer models, but equivocal effects in mouse mammary cancer models, and the observation that long-term maintenance of rats on a mixture of retinyl acetate and palmitate resulted in an increased incidence of mammary gland carcinomas. In addition, the cancer-preventive activity of retinyl esters in other sites and in other species was inadequate.

10.2 Overall evaluation

Serum retinol concentrations are homeostatically controlled across a wide range of intakes of both provitamin A carotenoids and preformed vitamin A. Research conducted on vitamin A using a wide variety of methods, from cell cultures *in vitro* and experimental models in animals to observational studies and randomized intervention trials in humans needs to be evaluated in terms of the overriding importance of this system of homeostatic control. Some research has been done in the setting of vitamin A deficiency, some in the setting of excess, and some in the wider range of normal intakes.

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 circultion (although they may well have influenced levels of more active metabolites in other tissues). The results of these studies have been largely negative, supporting the conclusion that for most cancer sites the preponderance 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, and 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 by preformed vitamin A following lung cancer, and this study was unusual in that it used very high doses of preformed vitamin A. It is important to note that all the previous trials of vitamin A chemoprevention in humans has been relatively

short-term studies, none extending beyond six years. If vitamin A is protective at earlier stages of carcinogenesis, as is suggested by studies which show that vitamin A can protect against genetic effects of other carcinogens *in vitro*, then longer trials 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 proven the benefits of correcting vitamin A deficiency for several conditions including total morbidity and mortality. A limited number of animal studies support the hypothesis that vitamin A deficiency might increase cancer risk. Confirmatory studies in vitamin A-deficient populations are lacking. The two cancer chemoprevention trials conducted among populations in China and India 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 enquiry will be covered in Volume 4 of this *IARC Handbook series*.

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