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VITAMIN A AND CANCER PREVENTION II: COMPARISON OF THE EFFECTS OF RETINOL AND β-CAROTENE

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Former blue asbestos workers known to be at high risk of asbestos-related diseases, particularly malignant mesothelioma and lung cancer, were enrolled in a chemo-prevention program using vitamin A. Our aims were to compare rates of disease and death in subjects randomly assigned to β-carotene or retinol. Subjects were assigned randomly to take 30 mg/day β-carotene (512 subjects) or 25,000 IU/day retinol (512 subjects) and followed up through death and cancer registries from the start of the study in June 1990 till May 1995. Comparison between groups was by Cox regression in both intention-to-treat analyses and efficacy analyses based on treatment actually taken. Median follow-up time was 232 weeks. Four cases of lung cancer and 3 cases of mesothelioma were observed in subjects randomised to retinol and 6 cases of lung cancer and 12 cases of mesothelioma in subjects randomised to β-carotene. The relative rate of mesothelioma (the most common single cause of death in our study) for those on retinol compared with those on β-carotene was 0.24 (95% CI 0.07–0.86). In the retinol group, there was also a significantly lower rate for death from all causes but a higher rate of ischaemic heart disease mortality. Similar results were found with efficacy analyses. Our results confirm other findings of a lack of any benefit from administration of large doses of synthetic β-carotene. The finding of significantly lower rates of mesothelioma among subjects assigned to retinol requires further investigation. ***Int. J. Cancer*** **75:362–367, 1998.**

Many epidemiological studies have demonstrated inverse relationships between dietary intake of β-carotene (pro-vitamin A) and lung cancer risk and between serum β-carotene levels and lung cancer risk (Fontham, 1990). A significant reduction in total mortality, and particularly stomach cancer mortality, for subjects taking a mixture of β-carotene, vitamin E and selenium was reported from a randomised intervention trial (Blot *et al.,* 1993). However, a prevention trial in Finland reported no reduction in incidence of lung cancer among men who received α-tocopherol and, unexpectedly, a significant 18% higher incidence of lung cancer among men who received β-carotene than among those who did not (ATBCCPSG, 1994). There then followed a similar finding in the CARET study (Omenn *et al.,* 1996).

Vitamin A (retinol) and other retinoids, while indicating mixed results in some preventive studies, have had some success in clinical trials, and all-*trans*-retinoic acid is now an accepted treatment for acute promyelocytic leukaemia (Frankel and Warrell, 1993).

Elevated total serum cholesterol is a known risk factor for ischaemic heart disease (IHD), and the incidence of IHD is related inversely to serum levels of high-density lipoprotein (HDL) cholesterol (Stamler, 1992). There is some evidence that β-carotene and other anti-oxidants may be helpful in increasing the proportion of HDLs in total cholesterol and possibly in reducing both major coronary and vascular events (Gaziano, 1994). In contrast, high doses of retinol are known to increase the proportion of LDL cholesterol and the risk of coronary disease (Dimery, 1993).

In an attempt to reduce the known elevated risks of malignant mesothelioma and lung cancer in former workers from the crocidolite (blue asbestos) mine and mill at Wittenoom Gorge in the Pilbara region of Western Australia (de Klerk *et al.,* 1989), an intervention primarily using vitamin A was established in 1990. The magnitude of the differences in mortality and cancer incidence between those joining the intervention program and those not joining is described in an accompanying article (Musk *et al.,* 1997).

Our study compares the efficacy of the 2 most common dietary forms of vitamin A, retinol and beta-carotene, in the prevention of malignant mesothelioma, lung cancer, IHD and other causes of death using a randomised trial in these former asbestos workers known to be at increased risk of asbestos- and smoking-related malignancies.

SUBJECTS

Selection into the study has been described in detail elsewhere (Musk *et al.,* 1997). Briefly, of the former workers known to be alive, 1,203 (1,111 men and 92 women) joined the program between June 1990 and May 1995, of whom 1,024 (947 men and 77 women) were eligible for this part of the study (*i.e.,* could attend the Perth Chest Clinic and were not women of child-bearing age). Five hundred and twelve subjects were randomised initially to receive retinol and 512 to receive β-carotene.

METHODS

All subjects residing in the Perth metropolitan area and accessible country areas attended the Perth Chest Clinic for induction into the study. Further attendance was then arranged annually. All subjects gave informed consent, and the study was approved by the Human Rights Committee of the University of Western Australia and the Clinical Drug Trials Committee of the Sir Charles Gairdner Hospital. Subjects completed a questionnaire on medical history and current and past smoking. Duration and intensity of asbestos exposure were known in detail from the ongoing cohort study of the Wittenoom workforce (de Klerk *et al.,* 1989). Usual dietary intake of vitamin A was assessed with a specially developed abbreviated food-frequency questionnaire (Ambrosini *et al.,* 1993) at both the 1st and 5th visits. A plain chest X-ray (standard posterior/anterior chest radiograph) was performed at the 1st and 5th visits. Venesection was carried out at every visit to measure liver function (plasma bilirubin, alkaline phosphatase, γ-glutamyl transferase and alanine aminotransferase) and plasma levels of

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β-carotene and retinol by high-performance liquid chromatography.

Subjects were allocated randomly to a supply of capsules (at least 400 days worth) of either β-carotene (30 mg/day as synthetic *trans*-β-carotene supplied by Roche Australia, Sydney, Australia) or retinol (25,000 IU/day as retinyl palmitate) by random numbers in blocks of 2. The 2 treatments were boxed identically but were not encapsulated identically, so while subjects were unaware which treatment they were actually receiving, they could tell if they were receiving the same or different treatment compared with other people on the trial. Also, staff could tell which treatment was being offered. It was considered that the advantages of double-blindness (or even complete single-blindness) in treatment allocation did not outweigh cost and logistic factors, especially as no placebo was involved and outcome was assessed objectively through official disease registers. A problem with printing the labels for the pill containers in the first 2 weeks of the study resulted in assignment of the wrong pills to 15 patients, 10 were given retinol in error and 5 β-carotene in error.

If any of the liver function tests were found to be abnormal, subjects were considered unsuitable for retinol therapy and withdrawn from the study. All subjects were provided with access to the study personnel to answer questions on possible toxicity, which was monitored annually using questionnaires, measurements of plasma vitamin A levels and liver function tests. Subjects reporting symptoms that they believed may have been related to their treatment were reassured and advised to see their usual medical practitioners. If they remained uncertain, they could suspend therapy for 4 weeks and report the effect on symptoms before restarting therapy or withdrawing. Participants were informed of their treatment if a side effect that may have resulted from retinol toxicity was reported. All such withdrawals, and those withdrawing after abnormal liver tests, were still included in the analysis as receiving their initial treatment allocation. Similarly, the 15 subjects incorrectly assigned the pills originally were included in the group to which they were assigned. Thus, the standard ''intention-to-treat'' analysis was the primary analysis performed. Subjects withdrawing because of problems with retinol could continue with β-carotene if they wished.

On their return visit at the end of the 1st year, subjects were asked to bring back their containers for pill-counting for compliance assessment. As all contained the requisite number, this practice subsequently was discontinued. Plasma carotene measurements provided further information on compliance with β-carotene, but plasma retinol does not reflect retinol intake. Retinyl palmitate itself could have been monitored solely for compliance (as in the CARET study [Omenn *et al.*, 1991]), but this would have necessitated analysing all samples twice and was not carried out because of the cost and because compliance was not considered an important issue for this study; *i.e.*, the effectiveness of the program was of more interest than the efficacy of a particular treatment. There was no reason to suppose that compliance would have been different in the 2 groups, though known side effects from retinol are more common than those from β-carotene; these are generally minor and would most likely occur within the 1st year.

Outcome assessment

Deaths and incident cases of cancer were documented from regular searches of the Western Australian Cancer Registry (including the Western Australian Mesothelioma Registry) and of the Registrar General's Office for Western Australia. Date of cancer incidence (for malignant mesothelioma and lung cancer) was taken to be the date of the first relevant pathology specimen, even though the diagnosis may have been confirmed later (this is standard practice in the Western Australian Cancer Registry). Subjects who withdrew from the program were still followed up by telephone or traced through next of kin, telephone and electoral roll searches. All subjects were followed up from their date of entry after the start of the study in June 1990 till May 31, 1995.

Statistical analysis

Comparison between groups was carried out using Cox regression with computer program SPSS for Windows (Norusis, 1993). Various statistical tests were used for these comparisons, and the following separate outcomes were examined: incidence of malignant mesothelioma, incidence of lung cancer, other cancer deaths, IHD deaths and deaths from all other causes. Analyses were performed with and without adjustment for variables known to be associated with outcome, such as smoking, exposure to asbestos, age and sex. All subjects were included with the treatment group to which they were allocated initially, and subsequent changes were ignored for the intention-to-treat analysis. All statistical tests were two-sided unless otherwise stated. For Fisher's exact test, both 1- and 2-sided *p* values were calculated because of the asymmetry of the tail probabilities when cell sizes are small (Oldham, 1968).

A second set of analyses was done to assess efficacy: each subject was assigned to the group for the treatment they were actually receiving 4 weeks previously, so those who had been removed from retinol were counted in the β-carotene group 4 weeks after they had transferred and the initially mis-allocated 15 subjects were considered to have taken the supplements they actually received. Similarly, subjects who had missed appointments and had not been given any supplements for 65 weeks were moved to a ''no-treatment'' group, and those who withdrew from all treatments were included in this group 4 weeks after withdrawal. This necessitated a time-dependent analysis for all subjects with a 4-week lag; thus, cases of disease arising 4 weeks or less after commencing the trial were excluded.

Expected numbers of cases of mesothelioma were estimated from the predictive equation developed for the whole Wittenoom cohort using known risk factors (de Klerk *et al.*, 1989):

$$\log [I(t)] = 3.35 \log (t) + 0.46 \log (d) + 0.21 \log (f) - 20.416$$

where I(t) is the incidence of mesothelioma at *t* years after first exposure to (f) fibres/ml of crocidolite for (d) days. The number of expected cases was then calculated as the sum, over all subjects, of the cumulative risk (CR) given the incidence rate I(t) for time in the study, from t_1 to t_2:

$$\begin{aligned} CR &= 1 - \exp\left[-\int_{t1}^{t2} I(t)\, dt\right] \\ &= 1 - \exp\{\exp[-20.416 + 0.46 \log (d) + 0.21 \log (f)] \\ &\quad \times [t_1^{4.35} - t_2^{4.35}]/4.35\} \end{aligned}$$

Because actual follow-up time was used from entry at time t_1 to exit at time t_2 (the end of the study or the time of intervening death or disease), no allowance was required for competing risks.

Because there was no placebo group in our study, the directionality of differences between groups in numbers of cases of mesothelioma was assessed by comparison with these expected numbers.

Study power

Initial planning for the study was based on (*i*) the expectation that there would be a 90% response rate by eligible subjects known to be living in Western Australia, (*ii*) current (as of 1986) incidence rates in the cohort for malignant mesothelioma and lung cancer and (*iii*) a 50% reduction in disease incidence for one treatment compared with the other. The results indicated that the trial would need to run for 5 years after accrual was complete to have 80% power of detecting such a difference between treatments as significant at the 5% level if both lung cancer and mesothelioma were affected or 4 years if all cancers were affected. Power calculations, based on the formula from Rubinstein *et al.* (1981), were done using Program Power (1987). A condition made by the funding agency was that there should be a full analysis of efficacy of either or both treatments at 5 years after the study start.

RESULTS

Subject characteristics

The mean age of these ex-workers at time of entry into the study was 57 years. There were 21% current smokers and 27% never smokers. Duration of exposure to crocidolite ranged from 1 day to over 15 years and time since first exposure from nearly 25 years to over 45 years (Table I). All of the measured risk factors for the diseases of interest were similar in the 2 treatment groups.

Accrual and follow-up

All subjects attended at least once at the Perth Chest Clinic, and 490 (48%) have had 4 annual follow-up visits; median follow-up times were 232 weeks for the group on β-carotene and 233 weeks for the group on retinol. The majority (57%) of the subjects were enrolled in the first 6 months of the program, with only 61 (6%) new subjects enrolling in the last 2.5 years of the study.

Side effects

A small number of subjects withdrew completely from the study because of possible side effects, and 56 subjects (54 on retinol) continued attendance but switched treatments, 45 because of abnormal liver function tests. Symptoms of numerous possible side effects were reported, but these did not appear to relate to either of the treatment strategies except for one person (on retinol). This person complained of headache, which was attributed to benign intracranial hypertension by a neurologist and improved following the cessation of retinol therapy.

TABLE I – SUBJECT CHARACTERISTICS, SMOKING AND CROCIDOLITE EXPOSURE LEVELS

	β-carotene median (range) or number (%)	Retinol median (range) or number (%)
Age (years)	56 (40–82)	57 (40–83)
Male	475 (93)	472 (92)
Cigarette smoking		
Current smokers	106 (21)	108 (21)
Ex-smokers	263 (51)	270 (53)
Never smokers	143 (28)	134 (26)
Crocidolite exposure		
Days of exposure	193 (2–5,647)	184 (1–2,495)
Years from first exposure to entry	30.5 (23.7–45.4)	30.2 (23.9–43.6)
Intensity of exposure (fibres/ml)	15 (1–130)	10 (1–130)
Total subjects	512	512

TABLE II – DIETARY INTAKE AND PLASMA LEVELS OF β-CAROTENE AND RETINOL THROUGHOUT THE STUDY, MEANS (STANDARD ERRORS), SUBJECTS COMPLETING 4 ANNUAL FOLLOW-UP VISITS

	β-carotene group	Retinol group
Number of subjects	241	249
Dietary intake, 1st visit		
β-carotene (μg/day)	5,957	6,053
Retinol (μg/day)	682.6	758.5
Dietary intake, 5th visit		
β-carotene (μg/day)	6,516	6,035
Retinol (μg/day)	557.2	615.2
Plasma levels, 1st visit		
β-carotene (μmol/l)	0.55	0.48
Retinol (μmol/l)	2.59	2.69
Plasma levels, 5th visit		
β-carotene (μmol/l)	2.94	1.13
Retinol (μmol/l)	2.76	3.05

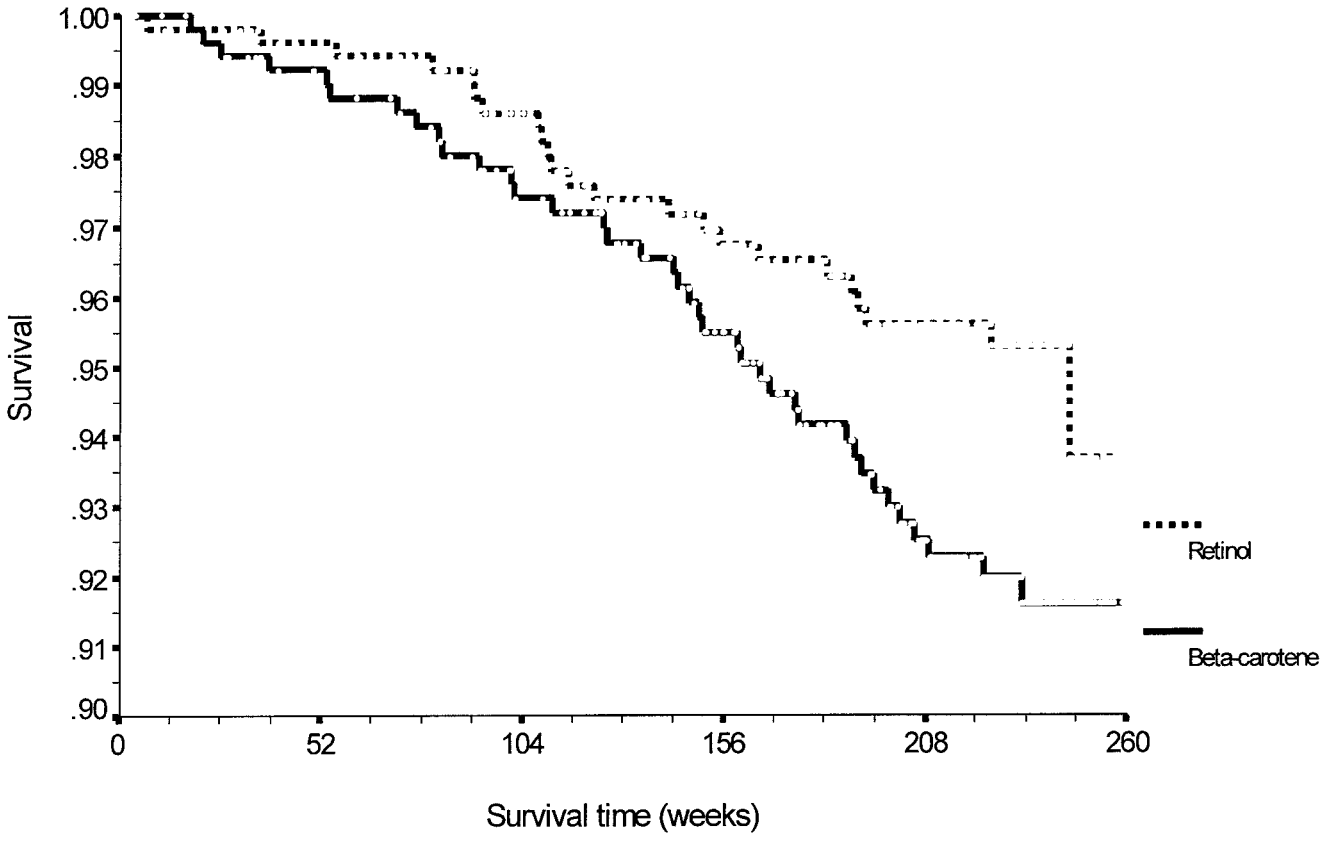

FIGURE 1 – Kaplan-Meier survival curve comparing all cause mortality between subjects originally randomised to β-carotene and subjects originally randomised to retinol.

Compliance and dietary intakes

Dietary intake of both β-carotene and retinol was similar in the 2 groups, and among those with 4 completed years, intake after 4 years was higher for β-carotene and significantly lower for retinol intake, possibly indicating overall changes in diet recommended by the local health department (Table II). There appeared to be good compliance in the β-carotene-treated group as judged by the initial increase in plasma levels and the lack of any decline thereafter (Table II). We have no reason to suppose that compliance was any different for the retinol-treated group. While not large, the increases in both plasma retinol and plasma β-carotene in the retinol group were statistically significant.

TABLE III – DEATH AND DISEASE ACCORDING TO RANDOMISED TREATMENT GROUP

	β-carotene	Retinol	RR for retinol (95% CI)
Malignant mesothelioma cases (4 living)	12	3	0.24 (0.07–0.86)
Lung cancer cases (4 living)	6	4	0.66 (0.19–2.32)
Deaths from other cancers	4	4	0.97 (0.24–3.90)
Ischaemic heart disease deaths	4	7	1.72 (0.50–5.86)
Deaths from other causes	15	7	0.46 (0.19–1.12)
All deaths	37	21	0.56 (0.33–0.95)

Mortality and cancer incidence

Malignant mesothelioma was the most common cause of death overall and arose more commonly in the group taking β-carotene (Table III). Two cases of malignant mesothelioma occurred shortly after entry at 3 and 5 weeks after randomisation and were included in the analysis. Apart from the incidence of mesothelioma and all deaths (see Fig. 1), outcomes of importance were not significantly different between the 2 treatment groups (Table III), though the β-carotene group had a lower rate of deaths from IHD.

Kaplan-Meier survival curves for the 2 groups for mesothelioma indicate that differences were not restricted to any period of follow-up (Fig. 2), and the 2 curves were significantly different ($p = 0.018$ by the log-rank test and 0.014 by the likelihood ratio test). The proportion of cases of mesothelioma in each group also was compared by Fisher's exact test, giving a p value of 0.020 (1-sided p value 0.017).

The hazard ratio with retinol compared to β-carotene for mesothelioma was 0.24 (95% confidence interval [CI] 0.07–0.86) and was unchanged after adjustment for age, sex, time since exposure to asbestos and duration of exposure to asbestos. For the ''all other deaths'' category, the hazard ratio was 0.46 (95% CI 0.19–1.12).

As a form of sensitivity analysis, log-rank tests were computed, assuming that further cases would arise in the retinol group during June 1995, the month following the finish date for this analysis. For

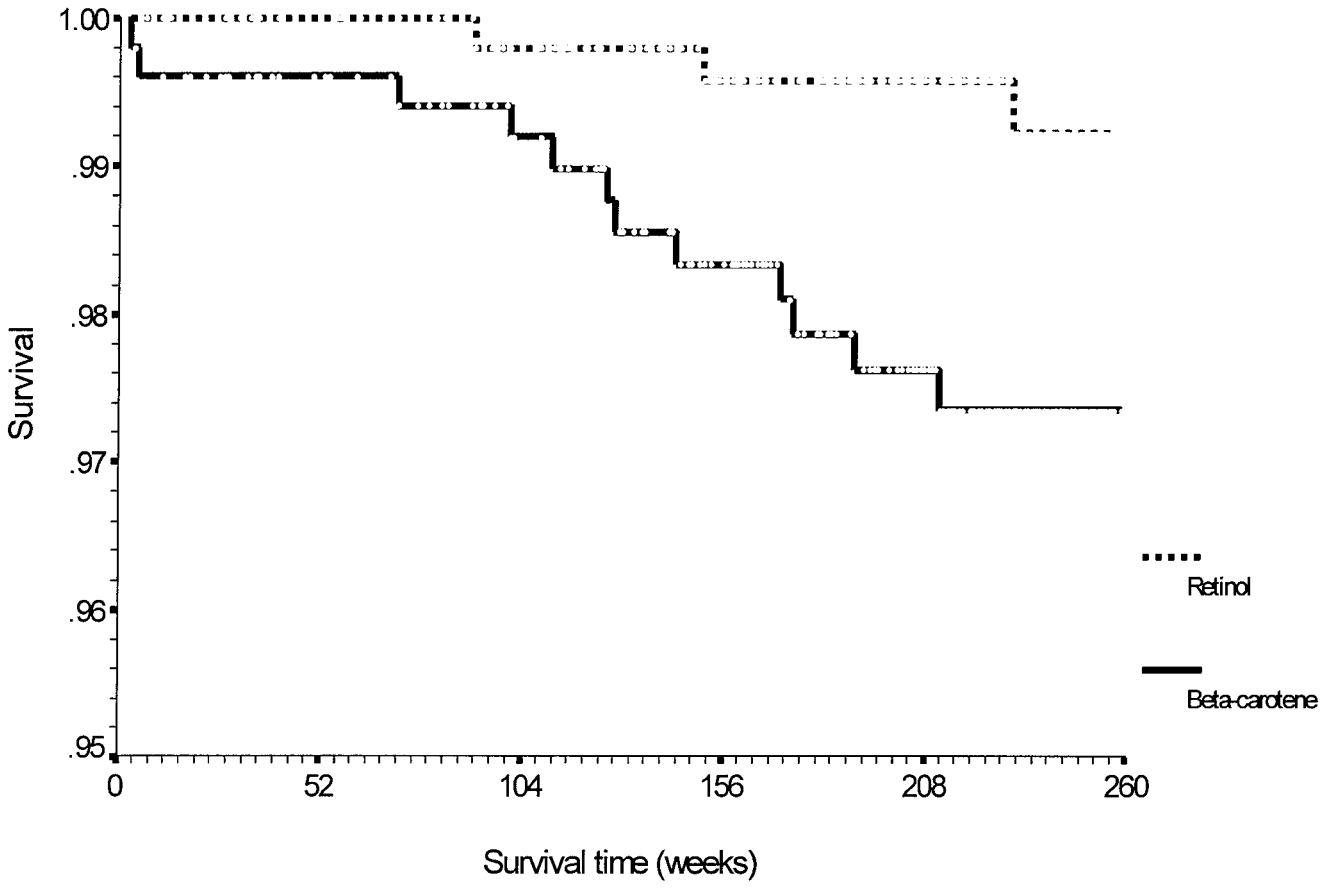

FIGURE 2 – Kaplan-Meier survival curve comparing mesothelioma-free survival between subjects originally randomised to β-carotene and subjects originally randomised to retinol.

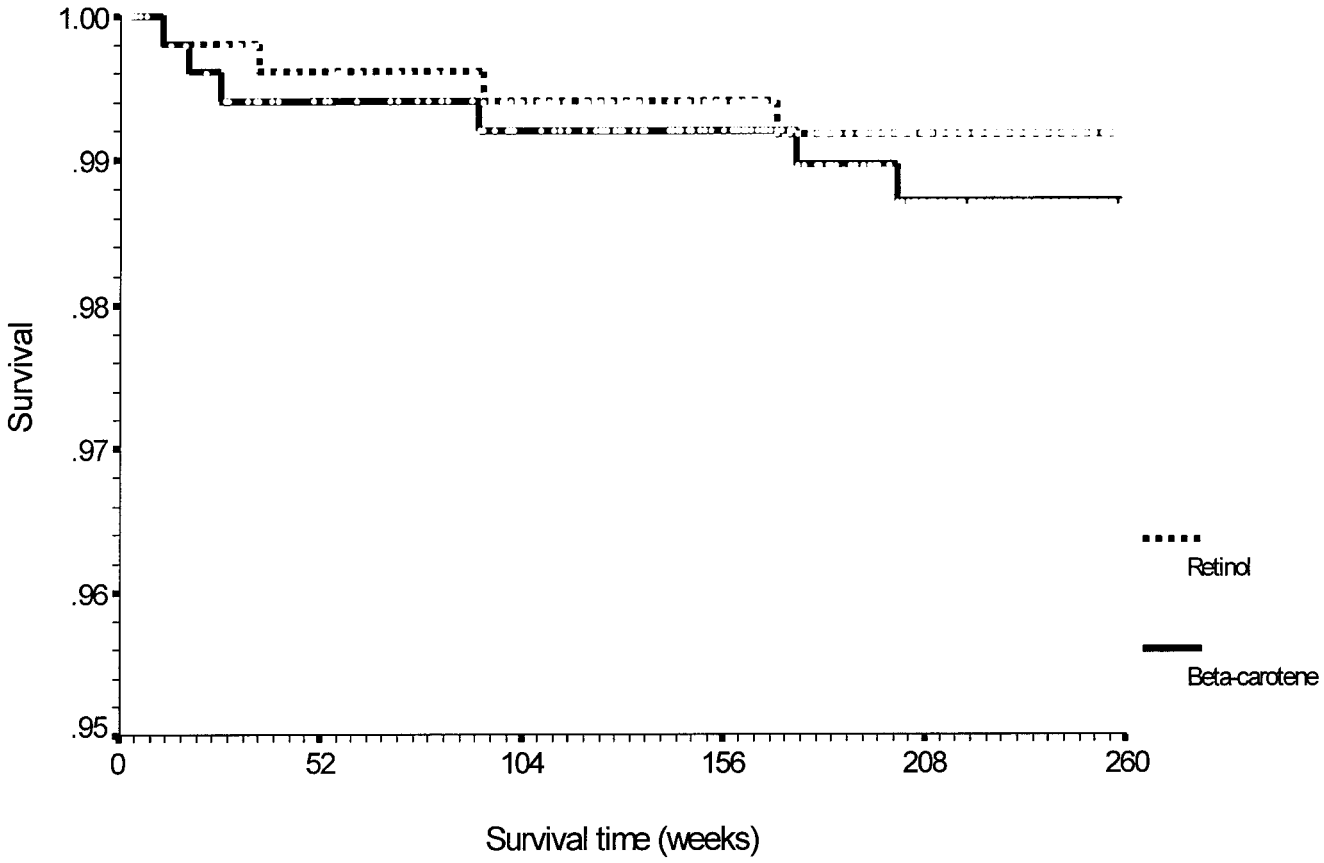

FIGURE 3 – Kaplan-Meier survival curve comparing lung cancer-free survival between subjects originally randomised to β-carotene and subjects originally randomised to retinol.

one more case in the retinol group (resulting in 12 in the β-carotene group and 4 in the retinol group) the *p* value would be 0.04, and for 2 more cases (resulting in 12 in the β-carotene group and 5 in the retinol group) the *p* value would be 0.08.

Two of the 3 cases of mesothelioma taking retinol were among the 54 subjects who switched to β-carotene. One changed after 1 month due to abnormal liver function and was diagnosed with mesothelioma nearly 3 years later; the other was changed due to side effects (skin irritation) after 4 years and was diagnosed 6 months later. The efficacy analysis therefore included these cases as if they were on β-carotene and excluded the case of mesothelioma (also on β-carotene) that arose 3 weeks after entry. The hazard ratio for retinol for this situation was 0.10 (95% CI 0.01–0.77) and that for ''no treatment'' was 0.67 (95% CI 0.15–3.08).

There was no significant difference in lung cancer incidence between groups (Table III, Fig. 3). One case of lung cancer was one of the 10 subjects randomised to β-carotene but actually given retinol. Efficacy analyses for this and other outcomes did not give results that were greatly different from the intention-to-treat analyses except that subjects who had stopped treatment (*i.e.,* had missed appointments) had higher mortality from other causes.

Based on the previously derived model for the incidence of mesothelioma, the numbers of expected cases of mesothelioma were 9.0 in the β-carotene group and 8.8 in the retinol group (Table IV); *i.e.,* there were significantly fewer cases of mesthelioma in the retinol group than expected. Among former workers living in Western Australia and not taking part in the program, 16 cases occurred up to the end of December 1994, when 17.9 were expected using the same model (notional $\chi^2 = 0.20$ on 1 df, $p = 0.65$). Among 176 subjects not able to attend at the clinic and who received β-carotene by mail, 2.9 cases were predicted and 3 cases occurred.

TABLE IV – OBSERVED AND EXPECTED CASES OF MALIGNANT MESOTHELIOMA IN RANDOMISED AND NON-RANDOMISED STUDY GROUPS UP TO MAY 31, 1995

Study group	Observed cases	Predicted cases
Retinol	3	8.8
β-carotene	12	9.0
Mailing group	3	2.9
Not in study (to end of 1994 only)	16	17.9

DISCUSSION

Our study confirms the results from other studies that the administration of synthetic β-carotene supplements confers no benefits and may be harmful. Furthermore, coupled with the estimates of expected numbers of cases of mesothelioma, our results suggest that retinol supplementation in subjects exposed to crocidolite may reduce the incidence of mesothelioma. In contrast, with similar numbers of lung cancers occurring in both treatment groups, there is no evidence of differing effects of retinol and β-carotene on lung cancer incidence. Significantly different effects of either intervention on mortality from IHD and from other disease also could not be demonstrated.

The results of the interventions on lung cancer incidence are consistent with neither β-carotene nor retinol having any protective effect or both agents having the same effect on this disease. This is

an acknowledged result of there being no placebo group in the trial. The decision to have no placebo group was deliberate and was made to maximise study response and power. It is possible that both agents increased the risk of lung cancer, and the results do not rule out as large an increase in risk of lung cancer for those taking β-carotene as that found in either the ATBC trial (ATBCCPSG, 1994), where β-carotene was the only treatment, or the CARET study (Omenn *et al.*, 1996), where both retinol and β-carotene were used.

The main result of interest in our study was the difference in incidence of mesothelioma between the 2 treatment groups. The relative immediacy and continuity of this difference when compared with the long ''latent period'' for mesothelioma implies that any effects (if real) are occurring at a late stage of the disease. This explanation is consistent with the successful implementation of retinoid therapy in certain cancers and in prevention of second cancers (Bollag and Holdener, 1992). Protective effects of β-carotene, if any, are more likely to act at very early stages of cancer initiation and would require longer follow-up to be demonstrated. This was one suggestion for explaining the unexpected findings in the Finnish study (ATBCCPSG, 1994). An alternative interpretation, that supplementation with β-carotene increases the incidence of mesothelioma, is not supported by the similarities in observed and expected numbers of cases in all groups in the whole program, excepting those taking retinol. These results are, however, compatible with there being a small increase in risk of mesothelioma for those on β-carotene (similar to that found in the CARET study) and a decrease in risk for those on retinol arising by chance alone.

Although as investigators we had no particular belief as to which, if either, of the treatments would be effective, the majority opinion at the time of starting the study probably would have favoured β-carotene, thus weakening the strength of the evidence for a real effect here. In favour of the finding being due to a real effect (and not a Type 1 error), however, are the following:

1. An analysis of actual treatment received in the efficacy analysis indicated an even stronger effect.
2. Rates of mesothelioma were the same as predicted in all worker groups not taking retinol (Table IV). Only in the retinol-treated group were mesothelioma rates unexpectedly low. Asbestos is the only confirmed risk factor for mesothelioma, and our ability to adjust for its effects considerably strengthens the reliability of the comparisons between observed and expected cases in the non-randomised groups. Additionally, the similarity of the observed and expected numbers of cases in all groups except the retinol-treated group means that the disease rate (allowing for temporal factors) in the retinol-treated group was significantly lower than the rate prior to the start of the study among the ''historical controls''.
3. Both animal and human studies indicate that retinol and other retinoids can be effective in controlling promotion of cancer at a late stage.

Few people will find our results conclusive. Furthermore, in the CARET study, where treatment subjects received both retinol and β-carotene, there were 14 mesothelioma cases in the treatment group compared with 9 in the placebo group, relative risk 1.52 (95% CI 0.66–3.52). While there still exists the possibility that retinol may exert some preventive effect on mesothelioma, it is clear that there is no benefit to be gained from the administration of synthetic *trans*-β-carotene supplementation. Accordingly, all subjects in the study have been advised to stop taking β-carotene, and further evaluation of the potential of retinol supplementation for prevention is continuing.

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