

# Lung cancer associated with beta-carotene supplementation in smokers 

- A meta-analysis of four randomised trials in a total of 109394 subjects showed a statistically significant increase in the risk of lung cancer among smokers who used dietary supplements containing beta-carotene, at a mean dose of $\mathbf{2 0}$ to $\mathbf{3 0} \mathrm{mg} /$ day. This contradicts the results of observational studies conducted in the 1990s.

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n the 1990s, observational studies suggested that a diet rich in fruit and vegetables could reduce the risk of lung cancer. Because of its antioxidant properties, it was thought that beta-carotene, a vitamin A precursor that is abundant in fruit and vegetables, might help prevent primary lung cancer. However, intervention studies of beta-carotene supplementation in smokers provided unexpected results: two of three randomised trials comparing beta-carotene supplementation with placebo or vitamin E supplementation showed a statistically significant increase in the incidence of lung cancer, while the third trial showed no difference (1).
A meta-analysis of clinical trials was published in 2008, and its conclusions remain valid.

A meta-analysis including more than 100000 subjects. A meta-analysis of 4 randomised controlled trials examined the relationship between beta-carotene supplementation and the risk of lung cancer (a)(2). A total of 109394 persons were enrolled: 54955 in the beta-carotene groups and 54439 controls. Betacarotene supplements of 20 to $30 \mathrm{mg} /$ day were taken for 2 to 12 years (2).
Lung cancer was more frequent in the beta-carotene groups (odds ratio 1.21, $95 \%$ confidence interval (CI) 1.09 to 1.34 ) (b).
Similar results were obtained in a more recent cohort study. The VITAL study (VITamins And Lifestyle) retrospectively analysed the effect of supplementation with beta-carotene, vitamin A, lutein or lycopene over a 10-year period in 77126 subjects aged 50 to 76 years. Those who took beta-carotene for at least 4 years had a three-fold increase in the risk of small cell lung cancer ( $95 \% \mathrm{Cl}$ : 1.29 to 8.07 ) (3).

Disturbing results in smokers. In smokers, beta-carotene supplementation was associated with a statistically significant increase in the risk of lung cancer (odds ratio $1.24 ; 95 \% \mathrm{Cl} 1.1$ to 1.39 ) (2).
In contrast, there was no statistically significant difference in the risk of lung cancer in the subgroups of former smokers (odds ratio 1.10; $95 \% \mathrm{Cl} 0.84$ to 1.45) or never-smokers (odds ratio 0.73; 95\% Cl 0.33 to 1.59).

In practice: beta-carotene supplementation is not advisable for smokers. There is strong evidence that betacarotene supplementation increases the risk of lung cancer, at least in smokers. Smokers who want to reduce their risk of developing lung cancer would be better advised to quit smoking rather than rely on beta-carotene supplements (4).

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$a$ - The 4 randomised trials analysed in this meta-analysis included the Women's Health Study and 3 trials (in a total of almost 70000 subjects) examined in issue 171 of Prescrire in 1997 (refs 1,2,5).
Details of the four trials:

- the double-blind ATBC trial (Alpha Tocopherol BetaCarotene Cancer Prevention Trial): 29133 Finnish male smokers aged 50 to 69 years who took beta-carotene $20 \mathrm{mg} /$ day or vitamin $E 50 \mathrm{mg} /$ day for a median of 6.1 years;
- the American CARET trial (Beta-Carotene and Retinol Efficacy Trial): 18314 smokers, former smokers or individuals exposed to asbestos, who took beta-carotene $30 \mathrm{mg} /$ day plus vitamin A 25000 IU/day for a median of 4 years;
- the Physicians' Health Study: a double-blind randomised placebo-controlled trial involving 22071 US male physicians aged 40 to 84 years who took beta-carotene 50 mg every other day for a median of 12 years;
- Women's Health Study: this double-blind randomised placebo-controlled trial involved 39876 US female healthcare professionals aged over age 45, 49\% of whom were current or former smokers. They took beta-carotene at a dose of $50 \mathrm{mg} /$ day every other day for a median of 2.1 years.
$b$ - The odds ratio is the ratio of the odds that an event will occur in one group to the odds that it will occur in another group. It provides a fair estimate of the relative risk of an event occurring provided some conditions are met (refs 6,7).

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2- Tanvetyanon T and Bepler G "Beta-carotene in multivitamins and the possible risk of lung cancer among smokers versus former smokers: a metaanalysis and evaluation of national brands" Cancer 2008; 113 (1): 150-157.
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## Benfluorex: yet more valve disorders

- Analysis of health insurance databases.

In November 2009, the French Health Products Safety Agency finally suspended marketing authorisation for benfluorex, due to the risk of cardiac valve disorders ( 1,2 ). Reports were increasing, and a French study based on hospital data confirmed the risks associated with this drug.

In 2009 the French national health insurance system conducted a study of one million diabetic patients, about 43000 of whom had been exposed to benfluorex (3). Compared to unexposed patients, those exposed to benfluorex in 2006 had approximately a 3 -fold increased risk of being hospitalised for valve failure in 2007, while in 2008 the risk of valve replacement surgery with extracorporeal circulation was about 4 times higher. Both increases were statistically significant.

This is an excellent example of how analysis of health insurance databases can contribute to improving patient safety.
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3- Cnamts "Benfluorex et valvulopathies cardiaques: une étude de cohorte sur l 048173 personnes traitées pour diabète" 9 November 2009: 13 pages.

