Increased free radical activity and high lipid oxidation impair glucose disposal in the peripheral tissues and exacerbate diabetic complications. These observations suggest a role for oxidative stress in the pathogenesis of type 2 diabetes mellitus (DM). Because of its extended system of conjugated double bonds, \(-\)carotene can scavenge peroxyl radicals and exert strong antioxidant activity, suggesting a protective effect against the development of type 2 DM.\(^6\),\(^7\)

Indirect evidence supporting such a protective role for \(-\)carotene comes from several observational studies relating increased intake of vegetables that are rich in carotenoids with a lower risk of type 2 DM.\(^8\)\(^-\)\(^10\) In addition, a recent dietary trial indicates that among people with impaired glucose tolerance, those assigned to a diet with more vegetables have a lower incidence of type 2 DM.\(^11\) It is possible, however, that the observed reduction in risk associated with vegetables rich in carotenoids may be due not to their \(-\)carotene content but rather to other nutrients in these foods or to other dietary or lifestyle factors. Moreover, biases due to selection of subjects, misclassification of exposure, and residual confounding cannot be fully addressed in observational studies,\(^12\) and no previous randomized trial has directly assessed the efficacy of \(-\)carotene to prevent type 2 DM.

To address this question, we examined the effect of long-term supplementation with \(-\)carotene on the incidence of type 2 DM in the Physicians’ Health Study, a randomized 12-year trial of 22,071 US male physicians.

**METHODS**

**Study Design**

The Physicians’ Health Study was a randomized, double-blind, placebo-controlled trial in which a 2×2 factorial design was used to evaluate the roles of aspirin and \(-\)carotene in the primary prevention of cardiovascular disease and cancer. The study’s methods have been detailed previously.\(^13\)\(^-\)\(^15\) In brief, at study entry in 1982, 22,071 male physicians aged 40 to 84 years were assigned randomly to receive as-

**Context**

Recent data suggest a protective role of carotenoids in the development of type 2 diabetes mellitus (DM), possibly via an antioxidant effect, but no randomized trial has directly assessed the efficacy of \(-\)carotene to prevent DM.

**Objective**

To determine whether long-term \(-\)carotene supplementation reduces the risk of developing type 2 DM.

**Design, Setting, and Participants**

A total of 22,071 healthy US male physicians aged 40 to 84 years in a randomized, double-blind, placebo-controlled trial, from 1982 to 1995. More than 99% of the participants had complete follow-up (median duration, 12 years).

**Intervention**

Subjects were randomly assigned to receive \(-\)carotene (50 mg on alternate days) or placebo.

**Main Outcome Measure**

Incidence of type 2 DM.

**Results**

A total of 10,756 subjects were assigned to \(-\)carotene and 10,712 to placebo. Incidence of type 2 DM did not differ between groups: 396 men in the \(-\)carotene group and 402 men in the placebo group developed type 2 DM (relative risk, 0.98; 95% confidence interval, 0.85-1.12). The lack of association between \(-\)carotene supplementation and incidence of type 2 DM persisted despite multivariate adjustment. There was no evidence of benefit when the period of risk was subdivided into years of follow-up or increasing duration of treatment.

**Conclusion**

In this trial of apparently healthy men, supplementation with \(-\)carotene for an average of 12 years had no effect on the risk of subsequent type 2 DM.
pirin alone, β-carotene alone (50 mg on alternate days), aspirin plus β-carotene, or both placebos. All men were free of a known history of myocardial infarction, stroke, or cancer. For the current analysis, we excluded 603 men who reported a history of diabetes before randomization. Thus, the final sample in this analysis was 21,468 men. Participants were mailed monthly packs that contained β-carotene or its placebo. The β-carotene component of the trial was terminated as scheduled on December 31, 1995. By the end of 1995, 99.2% of all participants were still taking the study pills, which continued through December 31, 1995. In this large-scale randomized trial among apparently healthy men, we detected no significant change in risk of type 2 DM associated with 12 years of β-carotene supplementation. The large sample size and long duration of the trial allowed for precise estimates with narrow 95% confidence intervals, excluding even a small effect of β-carotene.

### Statistical Analysis

For the current analysis, each participant accumulated follow-up time beginning at baseline and ending on the month of diagnosis of type 2 DM or censoring (death due to causes other than type 2 DM or December 31, 1995, whichever came first). We calculated incidence rates of type 2 DM by dividing the number of incident cases by person-years of follow-up. Relative risk was estimated by dividing the rate in the β-carotene group by the rate in the placebo group. We used Cox proportional hazards models to estimate the relative risk of developing type 2 DM adjusting for age, aspirin assignment, body mass index (calculated as weight in kilograms divided by the square of height in meters) (BMI), smoking status, alcohol intake, physical activity, history of high cholesterol level or hypertension, and use of multivitamins.

### RESULTS

There were no clinically or statistically significant differences between the 2 groups in terms of age, BMI, physical activity, cigarette smoking, alcohol consumption, or other variables (TABLE 1). After an average of 12 years of treatment and follow-up, no significant benefit of β-carotene on risk of type 2 DM was evident (TABLE 2). During the follow-up period, 396 incident cases of type 2 DM in the β-carotene and 402 cases in the placebo group were reported, for relative risk of 0.98 (95% confidence interval, 0.85-1.12). When the period of risk was subdivided by years of follow-up, no benefit was observed for any time period or duration of treatment (Table 2). The lack of association between β-carotene supplementation and occurrence of type 2 DM persisted in multivariate analysis adjusting for age, aspirin assignment, BMI, smoking status, alcohol intake, physical activity, cholesterol level, hypertension, and use of multivitamins.

### COMMENT

In theory, poor compliance with the assigned treatment or an inadequate dosage of β-carotene could explain the null findings. However, this explanation is unlikely. The rate of compliance with β-carotene treatment was 85% after 5 years and 78% after 12 years. The dosage of β-carotene increased serum β-carotene concentrations by approximately 4-fold.
This intake is roughly equivalent in its effect on blood levels to about 2 carrots a day and is above the level of dietary β-carotene consumption that is associated with benefit in observational studies.14

Underdiagnosis of type 2 DM may still be a concern because the study population was not screened for glucose tolerance and the diagnosis was self-reported. However, this is not a plausible explanation for our findings since all participants are physicians, who would be expected to report medical diagnoses accurately. A validation study of self-reported diabetes in the Nurses’ Health Study indicated a high correlation with medical record review.16 Given the randomized trial design, surveillance bias according to treatment assignment is unlikely. Moreover, the identical distribution of baseline characteristics in the β-carotene and placebo groups offers evidence that unknown confounding factors were distributed equally between the groups.

Three observational studies have examined the relation between plasma β-carotene level and degree of glucose intolerance or risk of type 2 DM.7,17,18 In a cross-sectional study of 109 hemodialysis patients, risk of diabetes was inversely related to plasma β-carotene concentration.17 In a nested case-control study of serum β-carotene and risk of type 2 DM, participants in the highest tertile of serum levels of β-carotene had a 55% lower risk of developing type 2 DM, but this association was greatly attenuated after controlling for cardiovascular risk factors.18 Finally, a significant inverse relation between serum β-carotene level and degree of glucose intolerance was observed in a random sample of 1665 US adults aged 40 to 74 years.7 Compared with participants with normal glucose tolerance, participants with impaired glucose tolerance had 13% lower β-carotene levels, and persons with newly diagnosed diabetes had levels about 20% lower \( (P = .004 \text{ for linear trend}) \). Plasma levels of other carotenoids, such as lycopene and cryptoxanthin, also were inversely related to glucose intolerance.

In several prospective cohort studies, increased consumption of vegetables was associated with reduced risk of type 2 DM.8-10 In a randomized trial of 577 people with impaired glucose tolerance who were followed up for 6 years in Da-Qing, China, those assigned to a diet with more vegetables had a 24% lower incidence of type 2 DM than the control group.11 This study, however, did not directly assess the efficacy of β-carotene in the prevention of type 2 DM. Although rich in β-carotene, vegetables have numerous other carotenoids that could affect risk of DM.

In conclusion, β-carotene supplementation had no effect on the risk of type 2 DM in this randomized trial of 12 years’ duration. The results of our study, however, should not be interpreted as completely refuting the findings of observational studies that increased intake of vegetables that are rich in carotenoids and other antioxidants may decrease the risk of type 2 DM. Our trial could not exclude the possibility that some carotenoids or other nutrients other than β-carotene are responsible for the observed association. Other antioxidants such as vitamin E may play a role in the prevention of type 2 DM, but their efficacy still needs to be evaluated in randomized trials.

### Table 2. Incident Cases of Type 2 Diabetes Mellitus According to Treatment Group and Years of Follow-up

<table>
<thead>
<tr>
<th>Follow-up Interval, y</th>
<th>Randomized Assignment</th>
<th>Placebo (n = 10712)</th>
<th>RR (95% CI)†</th>
<th>Multivariate-Adjusted RR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of study</td>
<td>396</td>
<td>402</td>
<td>0.98 (0.85-1.12)</td>
<td>0.99 (0.86-1.14)</td>
</tr>
<tr>
<td>1-2</td>
<td>84</td>
<td>94</td>
<td>0.89 (0.66-1.19)</td>
<td>0.90 (0.67-1.21)</td>
</tr>
<tr>
<td>3-4</td>
<td>72</td>
<td>63</td>
<td>1.14 (0.81-1.60)</td>
<td>1.21 (0.86-1.71)</td>
</tr>
<tr>
<td>1-4</td>
<td>156</td>
<td>157</td>
<td>0.99 (0.79-1.23)</td>
<td>1.02 (0.82-1.28)</td>
</tr>
<tr>
<td>≥3</td>
<td>312</td>
<td>308</td>
<td>1.01 (0.86-1.18)</td>
<td>1.02 (0.87-1.19)</td>
</tr>
<tr>
<td>5-9</td>
<td>176</td>
<td>170</td>
<td>1.03 (0.84-1.27)</td>
<td>1.02 (0.83-1.26)</td>
</tr>
<tr>
<td>≥10</td>
<td>64</td>
<td>75</td>
<td>0.85 (0.61-1.19)</td>
<td>0.86 (0.61-1.20)</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval.
†Adjusted for age, aspirin assignment, smoking status, alcohol intake, physical activity, body mass index, history of high cholesterol or hypertension, and use of multivitamins.