Dietary intakes of vitamins A, C, and E and risk of melanoma in two cohorts of women

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Within the two Nurses’ Health Study cohorts of US women, we examined whether higher intakes of vitamin C, vitamin E, retinol, or individual tocopherols or carotenoids are associated with a lower risk of melanoma. We confirmed 414 cases of invasive melanoma among over 162,000 Caucasian women aged 25–77 years during more than 1.6 million person-years of follow-up. Diet was measured every 4 years with a food frequency questionnaire and supplement use was reported every 2 years. Several measures of sun sensitivity were assessed and included in proportional hazards models. We found that vitamins A, C, E and their individual components were not associated with a lower risk of melanoma. Only retinol intake from foods plus supplements appeared protective within a subgroup of women who were otherwise at low risk based on nondietary factors (relative risk (RR) = 0.39, 95% confidence interval (CI) 0.22–0.71 for ≥1800 vs <400 μg day⁻¹, P for linear trend = 0.01). Contrary to expectation, we observed higher risks of melanoma with greater intakes of vitamin C from food only (RR = 1.43, 95% CI 1.01–2.00 for ≥175 vs <90 mg day⁻¹, P for linear trend = 0.05) and a significant positive dose–response with frequency of orange juice consumption (P = 0.008). Further research is needed to determine whether another component in foods such as orange juice may contribute to an increase in risk.

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The incidence of melanoma in the US is increasing at a greater rate than that of any other cancer site (Rigel, 1997), and this is considered real and not because of earlier detection or changes in diagnostic criteria (Dennis, 1999). Excessive exposure to sunlight is the primary environmental risk factor for melanoma (Elwood and Jopson, 1997; Osterlind et al, 1988). Ultraviolet (UV) radiation from the sun produces free radicals that may initiate carcinogenesis through oxidative damage to DNA, and antioxidant nutrients, such as carotenoids and vitamins E and C, can neutralize the free radicals or even suppress their creation (Di Mascio et al, 1991; Frei, 1994). In animals, β-carotene and α-tocopherol can inhibit skin tumours induced by UV light (Black and Chan, 1975). Preformed vitamin A (i.e., retinol) is necessary for the regulation of cell differentiation and can also reduce the incidence of skin tumours in animals exposed to UV light (Levine and Meyskens, 1980; Oikarinen et al, 1991). Certain carotenoids (e.g., α-carotene, β-carotene, β-cryptoxanthin) are metabolised to retinol. These retinol precursors along with antioxidant nutrients are prominent components of fruits and vegetables and may account for the observed anticancer effects of these foods (Ziegler, 1991).

Although antioxidants and retinol appear to be beneficial for some cancers, little is known about their effect on the development of melanoma. In case–control studies, lower risks of melanoma have been associated with higher blood levels of α-tocopherol (Knekt et al, 1991), β-carotene (Knekt et al, 1991), and retinol (Breslow et al, 1995), and with greater dietary intakes of vitamin E (Stryker et al, 1990; Bain et al, 1993; Kirkpatrick et al, 1994) and β-carotene (Bain et al, 1993). Only one prospective study of diet and melanoma has been reported and no associations were found for carotenoids, retinoids, or vitamins C and E (Veierod et al, 1997), although the questionnaire was inadequate for accurate assessment of these nutrients.

In this prospective study within two cohorts of women, we examined the risk of melanoma by intakes of vitamin C, vitamin E and specific tocopherols, retinol, and β-carotene and other carotenoids.

METHODS

Study populations

The Nurses’ Health Study (NHS) cohort consists of 121,700 female registered nurses living within 11 US states who were 30–55 years of age when they responded to the initial questionnaire in 1976. A second cohort of younger women, NHS II, was begun in 1989 with 116,671 nurses 25–42 years of age across 14 US states. Both studies were designed to examine prospectively the effects of lifestyle on risk of chronic disease. Information on individual characteristics, behaviours, and diagnosed diseases is collected with mailed questionnaires every 2 years and a response rate of at least 90%
has been attained in each follow-up cycle. Deaths are confirmed through the National Death Index (Stampfer et al., 1984).

A baseline food frequency questionnaire (FFQ) was included in the NHS and NHS II mailings in 1980 and 1991, respectively, and diet has been reassessed at least every 4 years. In this analysis, we used the 1984 FFQ as the baseline measure for the NHS cohort since it contained 38 fruits and vegetables, significantly more than the initial 1980 questionnaire (Feskanich et al., 2000).

The NHS and NHS II populations for this analysis consisted of those participants who completed an FFQ at baseline and who had no previous report of cancer (except nonmelanoma skin cancer). Owing to small numbers and low risk, non-Caucasian women were also excluded. After exclusions, 73,525 women remained in the NHS study population and 88,553 women remained in the NHS II study population.

Melanoma case confirmation

Within the study populations over the periods of follow-up for these analyses, 571 NHS women and 378 NHS II women reported a diagnosis of melanoma. Medical records were obtained for 486 (85%) of the NHS reports and for 289 (76%) of the NHS II reports; 254 (52%) and 160 (53%), respectively, were confirmed cases of invasive melanoma. These included superficial spreading and nodular types.

Diet and supplement use

For each food on the FFQ, women reported their frequency of intake during the past year in terms of a specified serving size. Daily dietary intakes of nutrients were calculated based on the nutrient content of foods derived primarily from US Department of Agriculture sources and supplemented with data from food manufacturers and published research. Total daily nutrient intakes were calculated by adding the amounts from multivitamins and specific supplements to the intakes from food. Use of nutrient supplements was assessed on each biennial questionnaire. For multivitamins, participants provided the name brand and the number of tablets taken per week. For vitamins C, E, and A (retinol) supplements, participants specified their daily dosage. For β-carotene supplements, reported use was assumed to be 6000 µg day\(^{-1}\).

Nutrient intakes were adjusted for total energy consumption (Willett and Stampfer, 1986) and these values were cumulatively updated in analyses to create the best estimates of long-term intake. That is, at the beginning of every 2-year follow-up cycle, each nutrient intake was calculated as the mean of all reported intakes up to that time.

Results from several validation studies in the NHS cohort indicate that nutrient intakes from the FFQ are valid for ranking subjects in diet analyses. In a comparison of the 1986 FFQ with two 1-week diet records, correlations were 0.79 for vitamin A from foods and 0.76 for vitamin C from foods (Willett, 1998). In other studies, vitamin E and β-carotene intakes from the FFQ predicted plasma levels of α-tocopherol (r = 0.55) (Stryker et al., 1988) and β-carotene (r = 0.31) (Michaud et al., 1998), respectively.

In the NHS cohort, a brief FFQ was included in the 1986 questionnaire for reporting food consumption during high school. These data were used to determine intakes earlier in life and to identify women with consistent intakes in high school and adult years.

Covariate information

In both cohorts, age, body weight, menopausal status, parity, and use of oral contraceptives or postmenopausal hormones were assessed in each 2-year follow-up cycle. Height was reported only on the initial questionnaire and was used to calculate body mass index (BMI, kg m\(^{-2}\)) in each cycle. Statistical analyses were also controlled for the following factors: skin reaction after two or more hours in the sun during childhood; number of sunburns over the lifetime (NHS) or between ages 15 and 20 (NHS II); number of moles on the left arm (NHS) or lower legs (NHS II); natural hair colour at age 21; family history (parent or sibling) of melanoma; and state of residence at cohort initiation. Information on frequency of sunscreen use was also collected, but was not used in analyses because it was unrelated to dietary intakes and was not independently associated with a decreased risk of melanoma.

Statistical analyses

The NHS and NHS II cohorts were analysed separately. Person-time was accrued for each participant from the return date of the baseline questionnaire (mailed June 1984 for NHS; June 1991 for NHS II) until a confirmed diagnosis of melanoma, a report of another cancer, death, or end of follow-up (1 June 1998 for NHS; 1 June 1999 for NHS II). Total person-years in analysis included 956,356 from NHS and 691,784 from NHS II.

Current diet and covariate data were used to allocate person-time to the appropriate category for each variable at the beginning of each 2-year follow-up cycle. Age-adjusted incidence rates were calculated within categories of diet and supplement use, and relative risks (RRs) were then calculated as the ratio of risk in each upper category compared to the risk in the lowest, or referent, category. We used proportional hazards models to adjust the RRs for all covariate information. To examine linear trend, dietary intakes were entered into models as continuous values.

To increase precision and to obtain a single summary of the results from NHS and NHS II, a random effects model (DerSimonian and Laird, 1986) was used to combine the RRs and to test for heterogeneity of results (P < 0.05).

RESULTS

Age-specific incidences of melanoma in the study populations were similar to national rates. For example, for white women 50–54 years of age, rates were 25 out of 100,000 year\(^{-1}\) in NHS and 27 out of 100,000 year\(^{-1}\) in recent US data (Ries et al., 2002).

Table 1 shows the characteristics of the study populations within low and high categories of vitamin C, vitamin E, retinol, and β-carotene intakes from foods plus supplements. For all nutrients, NHS women with higher intakes were older, and if postmenopausal, were more likely to use postmenopausal hormones. NHS II women with higher intakes were more likely to be nulliparous. In both cohorts, the nondietary risk factors for melanoma were not associated with nutrient intakes. Use of multivitamins and vitamin C and E supplements were high in both cohorts (53, 35, 36%, respectively, for NHS in 1998; 51, 27, 21%, respectively, for NHS II in 1999). Vitamin A (<5%) and β-carotene (<3%) supplement use were low in both cohorts.

We found no evidence that higher intakes of vitamin C, vitamin E, retinol, or β-carotene, the major carotenoid with provitamin A activity, are associated with a lower risk of melanoma (Table 2). Specific tocopherols (α-tocopherol, β-tocopherol, δ-tocopherol, γ-tocopherol) and other carotenoids, with or without provitamin A activity (z-carotene, lycopene, β-cryptoxanthin, lutein, and zeaxanthin), were also unrelated to risk (data not shown). Age-adjusted relative risks were only modestly attenuated when adjusted for the other melanoma risk factors.

Rather than the hypothesised inverse relation, we observed a positive association between dietary vitamin C and melanoma. Women with intakes ≥175 mg day\(^{-1}\) had an RR of 1.43 (95% CI 1.02–2.00) compared to those with intakes <90 mg day\(^{-1}\). The dose – response association was also marginally significant (P = 0.05). A significant linear relation remained when vitamin E, retinol, and β-carotene were added to the model (P = 0.03).
We also examined nutrient supplements in relation to melanoma risk (Table 3). Current use of multivitamins (a major source of retinol), and supplements of vitamins C and E were all unassociated with risk, and there was also no indication of benefit with longer duration of use. Vitamin A and β-carotene supplement use were too low to provide sufficient power for analysis.

Total fruits and vegetables or those with a high carotenoid content (>2000 IU serving−1) were also not associated with a lower risk of melanoma (Table 4) (see Feskanich et al (2000) for a description of the fruits and vegetables). However, consumption of fruits and vegetables high in vitamin C (>30 mg serving−1) was significantly associated with an increasing risk (P for linear trend = 0.01). Orange juice was the major contributor to dietary vitamin C (about 20% in both cohorts), and >1 serving day−1 was associated with an elevated risk of melanoma when compared to no orange juice consumption (RR = 1.61, 95% CI 0.92–2.84, P for linear trend = 0.008). In the NHS cohort, women recalled their intake of orange juice at one or both times (high school and college), and reported an RR of 1.59 (95% CI 1.17–2.18) and a dose-response of 0.04 per serving (P < 0.01) among all women. When analysed in the same model, significant positive dose–response relations were observed for both adult (P = 0.01) and high school (P = 0.04) orange juice consumption. In an analysis of consistent intake over time, women who reported that they consumed ≥1 serving day−1 of orange juice in both high school and as an adult had an RR of 2.32 (95% CI 1.36–4.00) compared to those who reported <1 serving week−1 in both time periods.

Since dietary vitamin C was not expected to be a risk factor for melanoma, we speculated that the positive associations might be because of greater sun exposure among women with higher vitamin C intakes. The highest incidences of melanoma were found among the NHS women who lived in Florida (43 out of 100,000 year−1) and California (31 out of 100,000 year−1), states where excessive sun exposure is more likely. However, their dietary intakes of vitamin C were not higher than the rest of the cohort and excluding them from analyses did not change results from those in Table 2 that were adjusted for state of residence.

Since nondietary determinants of melanoma contribute significantly to risk, we examined associations between vitamins A, C, E, and melanoma separately among women at higher and lower risk based upon nondietary factors. A total risk score was calculated using cohort-derived RRs associated with each of the five nondietary factors listed in Table 1. The lowest score of 5 was assigned to women with the lowest relative risk (RR = 1.0) for all factors; the highest risk scores were 11.9 in NHS and 14.3 in NHS II. Categories of low, middle, and high risk were defined to ensure that groups in the study populations had similar age distributions. When analysed in the same model, significant positive dose–response relations were observed for both adult (P = 0.01) and high school (P = 0.04) vitamin C consumption. In an analysis of consistent intake over time, women who reported that they consumed ≥1 serving day−1 of orange juice in both high school and as an adult had an RR of 2.32 (95% CI 1.36–4.00) compared to those who reported <1 serving week−1 in both time periods.

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### Table 2  Relative risks (RRs) of melanoma by daily intakes of vitamin C, vitamin E, retinol, and \( \beta \)-carotene

| Vitamin C (mg) | Cases | Person-years (thousands) | Age-adjusted \( ^{b} \) RR (95% CI\(^{d} \)) | Multivariate \( ^{c} \) RR (95% CI\(^{d} \)) |
|---------------|-------|--------------------------|---------------------------------|---------------------------------|
| Total\(^{a} \) |       |                          |                                 |                                 |
| \(< 1.10 \)   | 60    | 315                      | 1.00                            | 1.00                            |
| 1.10–1.59     | 89    | 363                      | 1.26 (0.73–2.19)                | 1.21 (0.71–2.06)                |
| 1.60–2.19     | 78    | 312                      | 1.31 (0.93–1.84)                | 1.21 (0.86–1.71)                |
| 2.20–2.99     | 81    | 323                      | 1.31 (0.93–1.85)                | 1.19 (0.84–2.68)                |
| \( \geq 4.00 \) | 106   | 335                      | 1.50 (0.78–2.89)                | 1.33 (0.74–2.38)                |
| \( \text{P for linear trend} \) |       |                          | 0.27                            | 0.53                            |

| Dietary\(^{f} \) |       |                          |                                 |                                 |
| \(< 9.0 \)      | 57    | 325                      | 1.00                            | 1.00                            |
| 9.0–11.4       | 73    | 307                      | 1.32 (0.93–1.87)                | 1.27 (0.90–1.80)                |
| 11.5–13.9      | 74    | 322                      | 1.29 (0.91–1.82)                | 1.24 (0.87–1.76)                |
| 14.0–17.4      | 112   | 353                      | 1.72 (1.24–2.37)                | 1.62 (1.17–2.25)                |
| \( \geq 17.5 \) | 98    | 341                      | 1.51 (1.08–2.11)                | 1.43 (1.02–2.00)                |
| \( \text{P for linear trend} \) |       |                          | 0.04                            | 0.05                            |

| Vitamin E (mg\(^{g} \)) |       |                          |                                 |                                 |
| Total\(^{a} \) |       |                          |                                 |                                 |
| \(< 9.0 \)      | 72    | 343                      | 1.00                            | 1.00                            |
| 9.0–10.9       | 85    | 317                      | 1.25 (0.77–2.04)                | 1.19 (0.75–1.90)                |
| 11.0–16.9      | 77    | 318                      | 1.15 (0.83–1.59)                | 1.05 (0.76–1.45)                |
| 17.0–24.9      | 89    | 357                      | 1.18 (0.68–2.07)                | 1.09 (0.64–1.83)                |
| \( \geq 50.0 \) | 91    | 313                      | 1.25 (0.70–2.23)                | 1.11 (0.66–1.85)                |
| \( \text{P for linear trend} \) |       |                          | 0.30                            | 0.54                            |

| Dietaty\(^{f} \) |       |                          |                                 |                                 |
| \(< 8.0 \)      | 75    | 324                      | 1.00                            | 1.00                            |
| 8.0–8.9        | 86    | 369                      | 0.99 (0.73–1.36)                | 0.96 (0.70–1.31)                |
| 9.0–9.9        | 103   | 385                      | 1.14 (0.85–1.54)                | 1.07 (0.79–1.44)                |
| 10.0–10.9      | 81    | 264                      | 1.30 (0.95–1.78)                | 1.21 (0.88–1.66)                |
| \( \geq 11.0 \) | 69    | 306                      | 0.93 (0.58–1.50)                | 0.88 (0.59–1.32)                |
| \( \text{P for linear trend} \) |       |                          | 0.80                            | 0.98                            |

| Retinol (\( \mu \)g) |       |                          |                                 |                                 |
| Total\(^{a} \) |       |                          |                                 |                                 |
| \(< 400 \)       | 87    | 322                      | 1.00                            | 1.00                            |
| 400–699         | 71    | 351                      | 0.75 (0.54–1.02)                | 0.72 (0.53–0.99)                |
| 700–999         | 78    | 317                      | 0.90 (0.66–1.23)                | 0.85 (0.63–1.16)                |
| 1000–1799       | 95    | 335                      | 1.03 (0.77–1.38)                | 0.97 (0.72–1.30)                |
| \( \geq 1800 \)  | 83    | 324                      | 0.92 (0.68–1.24)                | 0.85 (0.63–1.16)                |
| \( \text{P for linear trend} \) |       |                          | 0.80                            | 0.52                            |

| Dietary\(^{f} \) |       |                          |                                 |                                 |
| \(< 300 \)      | 79    | 309                      | 1.00                            | 1.00                            |
| 300–424         | 76    | 332                      | 0.90 (0.65–1.24)                | 0.88 (0.62–1.26)                |
| 425–599         | 95    | 368                      | 1.03 (0.76–1.39)                | 0.99 (0.73–1.35)                |
| 600–849         | 74    | 317                      | 0.91 (0.66–1.26)                | 0.87 (0.63–1.20)                |
| \( \geq 850 \)  | 90    | 323                      | 1.08 (0.75–1.56)                | 1.07 (0.74–1.55)                |
| \( \text{P for linear trend} \) |       |                          | 0.96                            | 0.99                            |

| \( \beta \)-Carotene\(^{h} \) (\( \mu \)g) |       |                          |                                 |                                 |
| Total\(^{a} \) |       |                          |                                 |                                 |
| \(< 2400 \)    | 56    | 320                      | 1.00                            | 1.00                            |
| 2400–3399      | 111   | 358                      | 1.75 (1.25–2.40)                | 1.67 (1.20–2.30)                |
| 3400–4399      | 73    | 320                      | 1.24 (0.79–1.93)                | 1.17 (0.79–1.73)                |
| 4400–5999      | 94    | 331                      | 1.54 (1.10–2.16)                | 1.44 (1.02–2.02)                |
| \( \geq 6000 \) | 80    | 320                      | 1.33 (0.92–1.93)                | 1.22 (0.86–1.74)                |
| \( \text{P for linear trend} \) |       |                          | 0.59                            | 0.96                            |

\(^{a}\)Results from NHS and NHS II were pooled to obtain risk estimates for the combined cohorts. All P-values were >0.05 in tests for heterogeneity. \(^{b}\)Relative risks were adjusted for age and follow-up cycle. In addition, dietary vitamin C was adjusted for vitamin C supplement use; dietary vitamin E was adjusted for vitamin E supplement use; and dietary retinol was adjusted for multivitamin use and vitamin A supplement use. \(^{c}\)Relative risks were adjusted for the covariates listed above plus the following: skin reaction after 2 h of sun exposure during childhood, number of sunburns over lifetime (NHS) or during teenage years (NHS II), number of moles on left arm (NHS) or on lower legs (NHS II), hair colour, family history of melanoma, state of residence, menopausal status, oral contraceptive use, postmenopausal hormone use, parity, height, and body mass index. \(^{d}\)95% confidence interval. \(^{e}\)Total nutrient intakes are from foods plus supplements. Dietary nutrient intakes are from foods only. \(^{f}\)Milligram of \( \alpha \)-tocopherol equivalents. \(^{g}\)\( \beta \)-carotene analyses for dietary intake were very similar to analyses of total intake because of low use of \( \beta \)-carotene supplements.
DISCUSSION

In this prospective study within two large cohorts of Caucasian women 25–77 years of age, we found little evidence that vitamin C, vitamin E, individual tocopherols, retinol, β-carotene, or other carotenoids are associated with a lower risk of invasive melanoma. The only inverse association that we observed was for total retinol intake when limited to women who were otherwise at low risk of melanoma based on nondietary factors. Although not an antioxidant, retinol is essential for regulating cell differentiation, and it is possible that it may only exert a notable effect without the overwhelming influence of other major risk factors. There is little prior research to support our finding. Breslow et al (1995) reported an RR of 0.4 when comparing extreme tertiles of plasma retinol levels, although there were only 30 melanoma cases in this analysis and results were not significant. Other case–control studies did not find an association between plasma (Stryker et al, 1990; Knekt et al, 1991) or dietary (Stryker et al, 1990; Kirkpatrick et al, 1994) levels of retinol and risk of melanoma. It is possible that our observed inverse association for total retinol intake among the low-risk women is a chance finding, but even if real, we would not recommend high retinol intakes for women at such low risk of melanoma since higher intakes have been associated with increased risk of hip fracture among postmenopausal women (Feskani et al, 2002).

An unexpected finding was the increased risk of melanoma with higher intakes of vitamin C from food, and more frequent consumption of fruits and vegetables high in vitamin C, particularly orange juice. It is possible that this, too, is a chance finding. However, given that this association was strongest among the higher risk sun-sensitive women, it is also possible that a photosensitising compound in these foods is responsible for the increased risk; vitamin C is unlikely to be responsible because supplement users were not at higher risk. Furocoumarins are naturally produced in fruits and vegetables in response to physical damage, fungal infection, and attack by pests, and they exhibit phototoxic effects because of their capacity to absorb photons and then release the energy to cause cellular damage (Gasparro et al, 1997). Plants of the umbelliferae family, such as parsnips, celery, fennel, and parsley, have a high furocoumarin content, and dermatologic reactions have been observed with ingestion of large quantities and subsequent exposure to UV radiation (Ljunggren, 1990; Puig and Demaragas, 1994). Some types of limes (Nigg et al, 1993) and oranges (Joint Food Safety and Standards Group, Food Standard Agency, UK, 1993) also contain appreciable quantities of furocoumarins and have been noted to trigger dermatologic reactions with ingestion.

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| Table 3 | Relative risks (RRs) of melanoma by use of vitamin supplements\textsuperscript{a} |
|----------|---------------------|---------------------|-------------------------------|
|          | Cases | Person-years (thousands) | Multivariate\textsuperscript{b} RR (95% CI) |
| vitamin A supplements | Never | 143 | 596 | 1.00 |
|                   | Past  | 83  | 302 | 0.96 (0.51–1.83)\textsuperscript{*} |
|                   | Current | 185 | 700 | 1.02 (0.82–1.28) |
| vitamin C supplements | Never | 231 | 973 | 1.00 |
|                   | Past  | 51  | 209 | 0.97 (0.71–1.32) |
|                   | Current | 129 | 416 | 1.07 (0.64–1.77)\textsuperscript{*} |
| vitamin E supplements | Never | 292 | 1189 | 1.00 |
|                   | Past  | 40  | 141 | 0.98 (0.70–1.38) |
|                   | Current | 79  | 268 | 1.02 (0.79–1.33) |

\textsuperscript{a}P<0.05 in test for heterogeneity of results from NHS and NHS II. \textsuperscript{b}Results from NHS and NHS II were pooled to obtain risk estimates for the combined cohorts.

| Table 4 | Relative risks (RRs) of melanoma by daily servings of fruits and vegetables and by frequency of consumption of orange juice\textsuperscript{a} |
|----------|---------------------|---------------------|---------------------|---------------------|
|          | Cases | Person-years (thousands) | Multivariate\textsuperscript{b} RR (95% CI) |
| Total fruits | <1.0 | 62  | 349  | 1.00 |
|           | 1.0–1.4 | 58  | 274  | 1.16 (0.80–1.66) |
|           | 1.5–2.4 | 151 | 524  | 1.42 (0.99–2.04) |
|           | 2.5–3.4 | 83  | 303  | 1.37 (0.95–1.98) |
|           | ≥3.5 | 60  | 198  | 1.37 (0.86–2.20) |
| P for linear trend | 0.22 |
| Total vegetables | <2.0 | 96  | 448  | 1.00 |
|           | 2.0–2.9 | 126 | 479  | 1.22 (0.92–1.62) |
|           | 3.0–3.9 | 106 | 356  | 1.32 (0.97–1.78) |
|           | 4.0–4.9 | 53  | 196  | 1.11 (0.76–1.62) |
|           | ≥5.0 | 43  | 169  | 1.01 (0.68–1.50) |
| P for linear trend | 0.81 |
| Fruits and vegetables high in carotenoids | <0.25 | 50  | 263  | 1.00 |
|           | 0.25–0.49 | 116 | 447  | 1.30 (0.51–3.33)\textsuperscript{*} |
|           | 0.50–0.74 | 85  | 347 | 1.18 (0.49–2.85)\textsuperscript{*} |
|           | 0.75–0.99 | 68  | 236 | 1.40 (0.73–2.68) |
|           | ≥1.00 | 95  | 355  | 1.24 (0.67–2.29) |
| P for linear trend | 0.78 |
| Fruits and vegetables high in vitamin C | <0.5 | 57  | 317  | 1.00 |
|           | 0.5–0.9 | 77  | 376  | 1.10 (0.77–1.55) |
|           | 1.0–1.4 | 96  | 378  | 1.33 (0.94–1.87) |
|           | 1.5–1.9 | 92  | 280  | 1.54 (1.06–2.22) |
|           | ≥2.0 | 92  | 297  | 1.43 (0.99–2.07) |
| P for linear trend | 0.01 |
| Orange juice\textsuperscript{a} | Never | 39  | 228  | 1.00 |
|           | 1–3 month\textsuperscript{–1} | 70  | 364  | 1.09 (0.73–1.62) |
|           | 1 week\textsuperscript{–1} | 44  | 197  | 1.31 (0.83–2.05) |
|           | 2–6 week\textsuperscript{–1} | 203 | 799  | 1.44 (1.00–2.08) |
|           | ≥1 day\textsuperscript{–1} | 147 | 499  | 1.61 (0.92–2.84) |
| P for linear trend | 0.008 |

\textsuperscript{a}P<0.05 in test for heterogeneity of results from the NHS and NHS II. \textsuperscript{b}Results from NHS (1984–1998) and NHS II (1991–1999) were pooled to obtain risk estimates for the combined cohorts. \textsuperscript{c}Relative risks were adjusted for the covariates listed in Table 2 footnote c plus total energy intake, multivitamin use, and use of vitamin C, vitamin E, and β-carotene supplements. \textsuperscript{d}95% confidence interval. \textsuperscript{e}Follow-up for NHS is 1980–1998.
Table 5  Relative risks (RR) of melanoma by daily intakes of dietary vitamin C and total retinol, stratified by risk based on nondietary factors

| Dietary Vitamin C (mg) | Low risk | Middle risk | High risk |
|------------------------|----------|-------------|-----------|
| Cases                  | P-Y      | RR (95% CI) | P-value   |
| <90                    | 22       | 1.00        |           |
| 90 – 114               | 24       | 1.15 (0.64 –2.07) |           |
| 115 – 139              | 17       | 0.78 (0.41 –1.49) |           |
| 140 – 174              | 32       | 1.29 (0.74 –2.25) |           |
| ≥ 175                  | 29       | 1.16 (0.65 –2.06) |           |
| P for linear trend     | 0.68     | 0.18        | 0.01      |

| Total Retinol (μg) | Cases | P-Y | RR (95% CI) | P-value |
|-------------------|-------|-----|-------------|---------|
| <400              | 38    | 162 | 1.00        |         |
| 400 – 699         | 22    | 186 | 0.51 (0.30 –0.86) |         |
| 700 – 1099        | 24    | 162 | 0.61 (0.28 –1.35) |         |
| 1100 – 1799       | 23    | 168 | 0.50 (0.29 –0.85) |         |
| ≥ 1800            | 17    | 160 | 0.39 (0.22 –0.71) |         |
| P for linear trend | 0.01  | 0.16 | 0.46      |         |

*Results from NHIS (1984 – 1998) and NHS II (1991 – 1999) were pooled to obtain risk estimates for the combined cohorts. All P-values were >0.05 in tests for heterogeneity. See text for description of risk score. †Relative risks were adjusted for the covariates listed in Table 2 footnote c. ‡Person-years of follow-up (thousands). §95% confidence interval. *P-value for interaction between risk score and nutrient intake.

In conclusion, higher intakes of vitamins C, E, and A were generally not associated with lower risks of melanoma in Caucasian women, although retinol may be protective among women who are otherwise at low risk of disease. Certain foods, such as orange juice, may be associated with an increased risk of melanoma, but further research is needed to confirm this finding and to identify the responsible constituents in these foods.

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