CANCER

Citrus intake and risk of skin cancer in the European Prospective Investigation into Cancer and Nutrition cohort (EPIC)

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Abstract

Citrus intake has been suggested to increase the risk of skin cancer. Although this relation is highly plausible biologically, epidemiologic evidence is lacking. We aimed to examine the potential association between citrus intake and skin cancer risk. EPIC is an ongoing multi-center prospective cohort initiated in 1992 and involving ~ 520,000 participants who have been followed-up in 23 centers from 10 European countries. Dietary data were collected at baseline using validated country-specific dietary questionnaires. We used Cox proportional hazards regression models to compute hazard ratios (HR) and 95% confidence intervals (CI). During a mean follow-up of 13.7 years, 8448 skin cancer cases were identified among 270,112 participants. We observed a positive linear dose–response relationship between total citrus intake and skin cancer risk (HR = 1.10, 95% CI 1.03–1.18 in the highest vs. lowest quartile; $P_{trend} = 0.001$), particularly with basal cell carcinoma (BCC) (HR = 1.11, 95% CI 1.02–1.20, $P_{trend} = 0.007$) and squamous cell carcinoma (SCC) (HR = 1.23, 95% CI 1.04–1.47, $P_{trend} = 0.01$). Citrus fruit intake was positively associated with skin cancer risk (HR = 1.08, 95% CI 1.01–1.16, $P_{trend} = 0.01$), particularly with melanoma (HR = 1.23, 95% CI 1.02–1.48; $P_{trend} = 0.01$), although with no heterogeneity across skin cancer types ($P_{homogeneity} = 0.21$). Citrus juice was positively associated with skin cancer risk ($P_{trend} = 0.004$), particularly with BCC ($P_{trend} = 0.008$) and SCC ($P_{trend} = 0.004$), but not with melanoma ($P_{homogeneity} = 0.02$). Our study suggests moderate positive linear dose–response relationships between citrus intake and skin cancer risk. Studies with available biomarker data and the ability to examine sun exposure behaviors are warranted to clarify these associations and examine the phototoxicity mechanisms of furocoumarin-rich foods.

Keywords Citrus · Cohort studies · Cutaneous melanoma · Epidemiology · Keratinocyte cancers

Abbreviations

BCCs	Basal-cell carcinomas
BMI	Body mass index
CIs	Confidence intervals
E3N	Etude Epidemiologique auprès de femmes de l'Education Nationale
EPIC	European Prospective Investigation into Cancer and Nutrition
HPFS	Health professionals follow-up study
HR	Hazard ratio
IARC	International Agency for Research on Cancer
KCs	Keratinocyte cancers
METs	Metabolic equivalents of task
NHS	Nurses' health study
PUVA	Psoralen and ultraviolet radiation A radiation
SCCs	Squamous-cell carcinomas

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SD Standard deviation
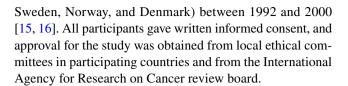UV Ultraviolet radiation

Introduction

Evidence suggests a potential association between citrus intake and skin cancer risk. Two large prospective cohort studies reported positive dose–response relationships between citrus consumption and the risks of cutaneous melanoma [1] and keratinocyte cancers [KC, including basal-cell (BCCs) and squamous-cell carcinomas (SCCs)] [2], in women from the Nurses' Health Study (NHS) and men from the Health Professionals Follow-Up Study (HPFS), respectively. In addition, recently, a large prospective cohort study of postmenopausal women suggested a positive association between citrus juice intake and melanoma risk [3]. These associations are highly plausible biologically [4–6], since citrus products are rich in furocoumarins such as psoralens [7], which exhibit carcinogenic and phototoxic effects [8]. Higher intake of total furocoumarins has indeed been reported to be associated with an increased risk of skin cancer, particularly of KCs, in the NHS and HPFS cohorts [9]. Oral administration of psoralen (methoxsalen) and UVA radiation (PUVA) has been used for many years to treat psoriasis and other skin diseases [10], and both experimental and epidemiologic studies suggested that long-term PUVA therapy increases skin cancer risk [11–13]. It has also been shown that psoralens and furocoumarins can interact with UV light to stimulate the proliferation of melanoma cells [14]. However, epidemiologic data showing an association are lacking.

Given the photosensitizing potential of furocoumarins and their known effects on skin, and given the intriguing associations described between citrus intake and skin cancer risk recently, a better understanding of the relationship between furocoumarin-rich foods and skin cancer risk is requested [4–6]. We sought to evaluate the associations between citrus consumption and skin cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study [15].

Methods

The EPIC cohort

EPIC is a multi-center prospective cohort study initiated in 1992. The rationale, full methods, and study design have been described in detail elsewhere [16]. Briefly, 521,448 participants mostly aged 25–70 years were recruited in 23 centers from 10 European countries (France, Italy, Spain, The Netherlands, United Kingdom, Greece, Germany, Sweden, Norway, and Denmark) between 1992 and 2000 [15, 16]. All participants gave written informed consent, and approval for the study was obtained from local ethical committees in participating countries and from the International Agency for Research on Cancer review board.

Dietary intakes

At baseline, dietary intakes over the 12 months before recruitment were assessed using validated country-specific dietary questionnaires designed to reflect local dietary patterns [17]. In the present study, the analyzed food groups were citrus fruits and citrus juices; these groups were analyzed overall, as no information on type of citrus fruit or juice was available in the cohort. Total intake of citrus was calculated as the sum of intakes of citrus fruits and juices, excluding centers in which no data were available on citrus juice intake (France, UK, and Norway). Detailed information on other lifestyle factors was collected using gender-specific questionnaires common to all study centers [18].

Follow-up and identification of cancer cases

Incident of cancer cases were identified through several methods, including record linkage with population-based cancer registries, health insurance records, pathology registries, and active follow-up of study subjects. Mortality data were obtained from cancer or mortality registries at the regional or national level. Skin cancer events were mostly ascertained through population-based cancer registries or pathology reports (96% of cases; melanoma: 92%; BCC: 96%; SCC: 99%), and a small proportion (4%) was identified from hospital admission and discharge records or national/regional mortality registries. Registration of KC cases may be incomplete in some centers because these cancers are not systematically recorded in cancer registries. Follow-up began on the date of recruitment and ended on the date of skin cancer diagnosis, date of death, date of emigration/loss of follow-up, or date of completion of the last returned questionnaire, whichever came first. Cancer incidence data were coded according to the International Classification of Diseases for Oncology (ICD-O-3). Cancer cases were defined as subjects with a first primary incident skin cancer (including KCs; C44). Information on stage, site, morphology, and grade of melanoma was collected from each center, where possible.

Study sample

Of the 521,448 participants, we first excluded prevalent cancer cases (including KCs) or subjects with missing information on date of diagnosis and follow-up information ($n = 29{,}456$), and those with missing information on

lifestyle factors (n = 6259) or extreme energy intake values (< 1st and > 99th percentiles of the distribution) (n = 9573). Because citrus consumption was our main exposure, and in order to conduct separate analyses for citrus fruit and juice and mutually adjust the models, we further excluded participants from the centers with no data on both citrus fruit and juice consumption (n = 206,048 including participants from France (n = 67,403), the UK (n = 75,416), Norway (n = 33,975), Naples (n = 4953), and Umea (n = 24,301)), leaving a final sample of 270,112 participants for analysis.

Statistical analysis

Statistical analyses were performed using the SAS package (version 9.4, SAS Institute). All significance tests were two-sided, $p < 0.05$ being considered statistically significant. Hazard Ratios (HRs) and 95% confidence intervals (CIs) of the risks of overall skin cancer, melanoma, BCC, and SCC associated with citrus intake were estimated using Cox proportional hazards regression models with age as the time scale. We first evaluated associations between total citrus intake and skin cancer risk, and then assessed the association with citrus fruit and citrus juice intakes separately. Citrus intake was estimated in grams per day and divided into quartiles. Tests for linear trend were performed by modeling quartiles of intake as a continuous variable. Multivariable analyses were performed with adjustment for potential confounders such as lifestyle and dietary factors, which were selected based on previously published data [1, 2, 19]. Models were first adjusted for age and stratified by study center, sex, and age at recruitment (Model 1), then additionally adjusted for body mass index, smoking status, alcohol intake at baseline, physical activity level [18], and total energy intake (Model 2). A third model additionally included intakes of total vegetables, non-citrus fruits and juices, and coffee intake for total citrus (Model 3). This model then included different factors according to the type of citrus exposure: based on Model 2, analyses on citrus fruit were additionally adjusted for intakes of total vegetables, non-citrus fruits, citrus juice, and coffee. Again based on Model 2, analyses on citrus juice were additionally adjusted for intakes of total vegetables, citrus fruit, non-citrus juice, and coffee. When data on categorical covariates were missing, a 'missing' category was introduced in the model.

Since the consumption of citrus products differs across European countries, we conducted stratified analyses by country, using country-specific tertiles of intake. However, we checked that using tertiles of intake in the overall population for each exposure did not change our findings (data not shown). The analyses were also stratified according to sex. Using hours of recreational outdoor physical activity (combining physical exercise, walking, cycling, and gardening) in summer as a proxy for hours of recreational sun

exposure, we evaluated potential effect modification by this factor using Wald tests. We further assessed the associations by tumor site and, for melanoma, histologic subtype, using competing-risk modeling, excluding cases with missing information on tumor characteristics for these analyses. Homogeneity tests were performed using Wald Chi square tests to compare estimates over tumor sites and types. Sensitivity analyses were carried out for the association between citrus fruit and skin cancer risk by including all study participants back in the analysis (including those from centers with no available data on citrus juice intake).

Results

During a mean follow-up of 13.7 years, 8448 skin cancer cases (melanoma: n = 1371; BCC: n = 5604; SCC: n = 1165, unknown type: n = 306) were identified among 270,112 participants. The mean intake of total citrus in the cohort was 90.9 g/day. Intakes varied across study locations, with the highest intakes observed in southern European countries (Spain, Italy, and Greece) and the lowest in Denmark (Table 1). Participants with high intakes of citrus were generally younger and more likely to be women, to have higher education and physical activity levels, and higher intakes of total energy, vegetables, non-citrus fruits, and non-citrus juices than those with low citrus intakes; however, they were less likely to be smokers and to consume alcohol and coffee (Table 2).

Total citrus intake was positively associated with skin cancer risk (HR = 1.10, 95% CI 1.03–1.18 for the highest quartile vs. the lowest, $P_{trend} = 0.001$), particularly with BCC (HR = 1.11, 95% CI 1.02–1.20, $P_{trend} = 0.007$) and SCC (HR = 1.23, 95% CI 1.04–1.47, $P_{trend} = 0.01$). We found no association with melanoma (HR = 0.98, 95% CI 0.83–1.15, $P_{trend} = 0.96$), although there was no heterogeneity across skin cancer types ($P_{homogeneity} = 0.14$) (Table 3).

When performing separate analyses for citrus fruit and juice, we found that citrus fruit intake was positively and linearly associated with skin cancer risk (HR = 1.08, 95% CI 1.01–1.16 for the highest quartile vs. the lowest, $P_{trend} = 0.01$), particularly with melanoma (HR = 1.23, 95% CI 1.02–1.48, $P_{trend} = 0.01$) (Table 4). However, while we found positively linear associations with BCC and SCC in the age-adjusted model, associations were no longer statistically significant after adjustment, again with no heterogeneity across cancer types ($P_{homogeneity} = 0.21$), although statistical significance remained in the fourth quartile of intake for SCC. Citrus juice intake was positively and linearly associated with skin cancer risk (HR = 1.08, 95% CI 1.01–1.16 for the highest quartile vs. the lowest, $P_{trend} = 0.004$), particularly with BCC (HR = 1.10, 95% CI 1.01–1.19, $P_{trend} = 0.008$) and SCC (HR = 1.23, 95% CI 1.05–1.44, $P_{trend} = 0.004$), but not with melanoma (HR

Table 1 Cohort characteristics by country, European prospective investigation into cancer and nutrition (EPIC) cohort study (n = 476,160)

	Cohort size	Mean age at recruitment[a]	Recruitment period range	Mean length of follow-up[a]	Women (%)	Total citrus intake (g/day)[a]	Citrus fruit intake (g/day)[a]	Citrus juice intake (g/day)[a]
Cohorts with available data on citrus juice and fruit intakes	270,112	52.3 (9.3)	1991–1999	13.7 (4.3)	60.3	90.9 (97.2)	56.3 (71.8)	34.6 (69.2)
Italy	39,592	50.5 (7.9)	1992–1998	13.9 (3.3)	64.5	110.9 (102.9)	84.7 (83.0)	26.1 (52.4)
Spain	39,989	49.2 (8.0)	1992–1996	15.8 (3.2)	62.2	115.8 (113.3)	99.0 (104.4)	16.3 (47.4)
The Netherlands	36,539	48.9 (11.9)	1994–1996	14.3 (3.3)	73.7	92.0 (76.5)	46.4 (40.4)	45.6 (59.4)
Germany	48,557	50.5 (8.5)	1994–1998	10.4 (3.2)	56.4	82.4 (106.5)	19.8 (19.3)	62.6 (102.6)
Denmark	55,014	56.6 (4.3)	1993–1997	14.4 (4.3)	52.2	64.5 (75.7)	35.0 (47.3)	29.6 (53.1)
Greece	26,048	53.1 (12.6)	1993–1999	10.8 (3.6)	58.5	99.7 (88.6)	95.6 (88.3)	4.1 (1.8)
Sweden	24,373	57.9 (7.5)	1991–1996	16.4 (5.6)	57.9	83.6 (100.9)	33.2 (35.3)	50.5 (92.4)
France	67,403	52.7 (6.6)	1993–1997	12.8 (3.5)	100	–	37.8 (40.5)	–
United Kingdom	75,416	51.6 (11.1)	1993–2001	14.7 (4.00)	69.7	–	43.2 (54.9)	–
Norway	33,975	48.3 (4.3)	1998	13.3 (2.5)	100	–	26.1 (37.0)	–
Naples	4953	50.5 (7.3)	1993–1997	15.0 (2.6)	100	–	87.8 (62.2)	–
Umea	24,301	47.7 (8.1)	1992–1996	16.5 (4.3)	50.5	–	51.3 (58.2)	–
All	476,160	52.0 (8.5)	1991–2001	13.8 (4.1)	70.1	–	49.5 (63.7)	–

SD standard deviation

[a]Mean (SD)

= 0.92, 95% CI 0.78–1.08, P$_{trend}$ = 0.31) (P$_{homogeneity}$ = 0.02) (Table 5). These results were not substantially different after adjustment for hours of recreational sun exposure during outdoor physical activity in summer (data not shown).

We found no evidence for effect modification by lifestyle factors on the associations between citrus intake and skin cancer risk (Supplementary Table S1), and no evidence for heterogeneity across countries (Supplementary Table S2) or sexes (Supplementary Table S3). In site-specific analyses, the positive associations between total citrus or citrus fruit intake and BCC risk were stronger for trunk tumors versus those of the head, neck, and extremities (P$_{homogeneity}$ = 0.04 and 0.02, respectively) (Supplementary Table S4); however, we detected no heterogeneity across sites for melanoma and SCC, or in subtype-specific analyses (Supplementary Table S5).

When participants from centers with no available data on citrus juice intake were included back in the analysis (total study sample: n = 476,160), associations between citrus fruit intake and the risks of total skin cancer, BCC or SCC remained, although slightly reduced (Supplementary Table S6). However, a positive association with melanoma risk was no longer observed.

Discussion

In this large European prospective study, we found a modest positive relationship between total citrus intake and skin cancer risk. Specifically, high intakes of citrus fruit were associated with higher melanoma risk, while citrus juice intake was positively and linearly associated with BCC and SCC risks.

To date, only three US prospective cohort studies explored the associations between citrus intake and skin cancer risk [1–3]. In the NHS and HPFS cohorts, higher intakes of citrus were associated with higher skin cancer risk [1, 2]; specifically, participants who consumed citrus over 1.6 times per day had 36%, 16%, and 21% higher risks of melanoma, BCC, and SCC, respectively, compared with those who consumed citrus less than twice per week. Consistently, our findings suggested that higher intakes of citrus (i.e. the fourth (mean = 217.5 g/day) versus the first (mean = 10.8 g/day) quartile of consumption) were associated with 11% and 23% higher risks of BCC and SCC, respectively. However, we did not find an association with melanoma risk, although with no detected heterogeneity across cancer types, which is consistent with the results from the Women Health Initiative (WHI) that reported no association between total citrus intake and melanoma risk after adjustment for known skin cancer risk factors [3]. Nevertheless, we observed that participants in the highest quartile of citrus fruit intake (mean = 147.5 g/day) had a 23% increased melanoma risk compared with those in the first (mean = 4.4 g/day), with a positive linear trend. There was also a positive association between citrus fruit intake and SCC risk but not BCC risk. In contrast, while citrus juice intake was not associated with melanoma risk, we found positive and linear associations with BCC and SCC risks. Unfortunately, we were unable

Table 2 Baseline characteristics of study participants according to quartile of total citrus intake, EPIC cohort (n = 270,112)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Participants (n)	67,527	67,603	67,454	67,528
Mean (SD) of total citrus intake (g/day)	10.83 (7.72)	44.20 (11.0)	90.90 (15.9)	217.5 (112.7)
Women (%)	50.3	59.9	65.0	65.9
Age at recruitment (years)	53.5 (8.8)	52.1 (9.4)	52.0 (9.6)	51.7 (9.3)
Body mass index, kg/m[b] (%)				
<18.5	1.0	0.8	0.6	0.6
18.5–24.9	39.8	41.6	40.0	38.8
25–29.9	41.8	40.7	40.8	41.8
≥30	17.4	16.9	18.6	18.8
Education (%)				
None/primary	43.0	37.2	41.6	41.7
Technical/secondary school	38.8	40.8	38.3	37.2
University degree	17.9	21.8	19.8	20.8
Unknown	0.3	0.2	0.3	0.3
Smoking (%)				
Never smoker	35.8	43.6	47.9	48.8
Former smoker	28.8	28.7	26.8	26.4
Current smoker	35.0	27.0	24.4	24.0
Unknown	0.4	0.6	0.9	0.8
Alcohol intake, g/day (%)				
Non-consumer	13.0	12.4	14.8	17.6
>0–2.09	14.2	16.3	18.1	17.8
2.10–7.14	16.5	18.5	18.6	18.6
7.15–17.30	22.4	23.6	22.5	21.4
>17.31	33.9	29.2	25.9	24.6
Physical activity (%)				
Inactive	20.8	19.4	16.6	16.2
Moderately inactive	30.6	27.4	25.4	25.4
Moderately active	38.2	41.0	45.0	45.9
Active	8.8	10.0	11.0	10.9
Missing	1.6	2.3	2.0	1.6
Total energy intake (kcal/day)[a]	2085.4 (632.2)	2097.71 (619.9)	2142.46 (623.3)	2259.5 (659.2)
Coffee (g/day)[a]	535.25 (475.6)	428.30 (402.8)	358.47 (370.3)	320.0 (342.0)
Vegetable (g/day)[a]	159.24 (115.9)	181.14 (128.5)	215.99 (151.5)	225.5 (166.5)
Citrus juice (g/day)[a]	3.12 (4.4)	13.10 (15.0)	28.27 (32.9)	93.9 (113.1)
Citrus fruit (g/day)[a]	7.71 (6.6)	31.10 (16.4)	62.62 (33.0)	123.6 (108.0)
Non-citrus fruit (g/day)[a]	113.42 (113.6)	153.50 (105.7)	201.02 (120.2)	248.3 (172.4)
Non-citrus juice (g/day)[a]	18.71 (74.1)	28.99 (75.9)	32.17 (75.2)	45.6 (108.3)

EPIC European Prospective Investigation into Cancer and Nutrition, *SD* standard deviation

[a]Mean (SD)

to examine associations by type of citrus fruit or juice, since this information was not available in the EPIC cohort. However, in the NHS and HPFS cohorts, associations were restricted to grapefruit for citrus fruit, and to orange juice for citrus juice [1, 2]. In contrast with our findings, the WHI study reported non-significant inverse association between citrus fruit intake and melanoma risk among postmenopausal women [3]. An Italian hospital-based case–control study also reported an inverse association between citrus fruit consumption and melanoma risk among 304 cases and 305 controls [20]; however, diet was assessed retrospectively in that study and thus subject to recall bias.

The three previous prospective studies suggested a possible interaction by UV exposure on these associations [1, 2]. Although we observed no interaction between citrus intake and hours of summer recreational outdoor physical activity

Table 3 Hazard ratios (HRs) and 95% confidence intervals (CIs) for intake of total citrus and risk of skin cancer, EPIC cohort (n = 270,112)

	Total citrus intake				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend
N	67,527	67,603	67,454	67,528	
Mean (g/day)	10.8	44.2	90.9	217.5	
Skin cancer					
No cases	2586	2119	1955	1788	
Age-adjusted HR (95% CI)	1 (ref)	1.11 (1.05–1.18)	1.17 (1.10–1.25)	1.17 (1.10–1.24)	< 0.0001
Multivariable-adjusted HR[a] (95% CI)	1 (ref)	1.08 (1.02–1.15)	1.13 (1.06–1.20)	1.12 (1.05–1.19)	0.0001
Multivariable-adjusted HR[b] (95% CI)	1 (ref)	1.07 (1.01–1.13)	1.11 (1.04–1.19)	1.10 (1.03–1.18)	0.001
Melanoma					
No cases	395	340	323	313	
Age-adjusted HR (95% CI)	1 (ref)	1.01 (0.87–1.17)	1.09 (0.94–1.27)	1.04 (0.89–1.21)	0.44
Multivariable-adjusted HR[a] (95% CI)	1 (ref)	0.98 (0.85–1.14)	1.05 (0.90–1.23)	1.00 (0.85–1.17)	0.78
Multivariable-adjusted HR[b] (95% CI)	1 (ref)	0.97 (0.83–1.13)	1.03 (0.88–1.21)	0.98 (0.83–1.15)	0.96
BCC					
No cases	1797	1416	1290	1101	
Age-adjusted HR (95% CI)	1 (ref)	1.12 (1.05–1.21)	1.17 (1.09–1.26)	1.17 (1.08–1.27)	< 0.0001
Multivariable-adjusted HR[a] (95% CI)	1 (ref)	1.09 (1.01–1.17)	1.12 (1.05–1.21)	1.12 (1.03–1.21)	0.001
Multivariable-adjusted HR[b] (95% CI)	1 (ref)	1.08 (1.00–1.16)	1.11 (1.03–1.20)	1.11 (1.02–1.20)	0.007
SCC					
No cases	312	282	262	309	
Age-adjusted HR (95% CI)	1 (ref)	1.14 (0.97–1.34)	1.21 (1.02–1.44)	1.28 (1.09–1.51)	0.002
Multivariable-adjusted HR[a] (95% CI)	1 (ref)	1.12 (0.95–1.32)	1.18 (1.00–1.41)	1.25 (1.06–1.48)	0.007
Multivariable-adjusted HR[b] (95% CI)	1 (ref)	1.11 (0.94–1.31)	1.17 (0.98–1.39)	1.23 (1.04–1.47)	0.01

Age-adjusted: adjusted for age and stratified by study center, sex, and age at recruitment

BCC basal-cell carcinoma, *CI* confidence intervals, *EPIC* European Prospective Investigation into Cancer and Nutrition, *HR* hazard ratio, *SCC* squamous-cell carcinoma

[a]Stratified by study center, sex, age at recruitment, and adjusted for education (none, primary school, technical/professional school, secondary school, university or higher degree), body mass index (BMI; < 25, 25–29, or ≥ 30 kg/m^2), smoking (never, former, and current), alcohol intake (non-consumer, then categorized in quartiles, g per day), physical activity (metabolic equivalent of task [MET] hour/week), and energy intake (continuous)

[b]Additionally adjusted for total vegetable intake (tertiles), coffee intake (tertiles), non-citrus fruit intake (tertiles), and non-citrus juice intake (tertiles). P$_{homogeneity}$ for total citrus and skin cancer type was 0.14

(which we used as a proxy for recreational sun exposure) in our analysis, the association appeared to be stronger for SCC among participants with higher levels of this variable. While this proxy incompletely reflects sun exposure, our findings lend support to those from the NHS and HPFS cohorts, which suggested that the positive associations between citrus intake and melanoma and SCC were stronger among participants with higher chronic sun exposure, those with a higher susceptibility to sunburn during childhood/adolescence, those with higher numbers of blistering sunburns, and those with higher annual residential UV flux. Also, our findings support those from the WHI study, in which an increased melanoma risk was observed in relation to citrus juice intake only among women who spent the most time outdoors in summer.

Citrus products are widely consumed foods; the major citrus fruits consumed in Europe are oranges, followed by clementines/tangerines, grapefruit, and lemons [21]. A potential mechanism underlying the observed associations could be based on the presence in citrus of psoralens and furocoumarins, a well-known class of photosensitizers with potential photocarcinogenic properties [22, 23]. Indeed, the NHS and HPFS cohorts have recently confirmed that participants with a high intake of total furocoumarins had higher risks of skin cancer, particularly of KCs [9]. Specifically, higher intakes of bergaptol, bergapten, 6′,7′-dihydroxybergamottin, and bergamottin were also significantly associated with increased KC risk. Furocoumarins are found naturally in the fruit peel, roots, and leaves of citrus products. Average estimated intakes of furocoumarins in the US and Germany are of 1.3 and 0.6 mg per day, respectively, and grapefruit is estimated to contribute to around 73% of furocoumarin intake from foods in the Western diet [24, 25]. Animal studies suggested that psoralen in the presence of

Table 4 Hazard ratios (HRs) and 95% confidence intervals (CIs) for intake of citrus fruit and risk of skin cancer, EPIC cohort (n = 270,112)

	Citrus fruit intake				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend
N	67,297	67,756	67,531	67,528	
Mean (g/day)	4.4	20.2	52.8	147.5	
Skin cancer					
No cases	2540	1968	2126	1814	
Age-adjusted HR (95% CI)	1 (ref)	1.08 (1.02–1.15)	1.14 (1.07–1.21)	1.15 (1.08–1.23)	< 0.0001
Multivariable-adjusted HR[a] (95% CI)	1 (ref)	1.04 (0.98–1.11)	1.10 (1.04–1.17)	1.12 (1.04–1.19)	0.0003
Multivariable-adjusted HR[b] (95% CI)	1 (ref)	1.03 (0.97–1.09)	1.07 (1.01–1.15)	1.08 (1.01–1.16)	0.01
Melanoma					
No cases	360	359	364	288	
Age-adjusted HR (95% CI)	1 (ref)	1.07 (0.92–1.24)	1.20 (1.03–1.39)	1.27 (1.07–1.51)	0.002
Multivariable-adjusted HR[a] (95% CI)	1 (ref)	1.04 (0.90–1.21)	1.16 (1.00–1.36)	1.24 (1.04–1.47)	0.007
Multivariable-adjusted HR[b] (95% CI)	1 (ref)	1.05 (0.90–1.22)	1.17 (0.99–1.37)	1.23 (1.02–1.48)	0.01
BCC					
No cases	1817	1213	1372	1202	
Age-adjusted HR (95% CI)	1 (ref)	1.06 (0.98–1.14)	1.13 (1.05–1.21)	1.10 (1.01–1.19)	0.003
Multivariable-adjusted HR[a] (95% CI)	1 (ref)	1.01 (0.94–1.09)	1.09 (1.01–1.17)	1.06 (0.97–1.15)	0.06
Multivariable-adjusted HR[b] (95% CI)	1 (ref)	0.99 (0.92–1.07)	1.05 (0.98–1.14)	1.02 (0.94–1.11)	0.37
SCC					
No cases	282	332	297	254	
Age-adjusted HR (95% CI)	1 (ref)	1.24 (1.05–1.46)	1.11 (0.93–1.31)	1.33 (1.10–1.60)	0.01
Multivariable-adjusted HR[a] (95% CI)	1 (ref)	1.22 (1.03–1.43)	1.08 (0.91–1.29)	1.30 (1.08–1.57)	0.03
Multivariable-adjusted HR[b] (95% CI)	1 (ref)	1.18 (1.00–1.40)	1.05 (0.88–1.25)	1.26 (1.03–1.54)	0.10

Age-adjusted: adjusted for age and stratified by study center, sex, and age at recruitment

BCC basal-cell carcinoma, *CI* confidence intervals, *EPIC* European Prospective Investigation into Cancer and Nutrition, *HR* hazard ratio, *SCC* squamous-cell carcinoma

[a]Stratified by study center, sex, age at recruitment, and adjusted for education (none, primary school, technical/professional school, secondary school, university or higher degree), body mass index (BMI; < 25, 25–29, or ≥ 30 kg/m²), smoking (never, former, and current), alcohol intake (non-consumer, then categorized in quartiles, g per day), physical activity (metabolic equivalent of task [MET] hour/week), and energy intake (continuous)

[b]Additionally adjusted for total vegetable intake (tertiles), non-citrus fruits (tertiles), citrus juice (tertiles) and coffee intake (tertiles). P$_{homogeneity}$ for citrus fruit and skin cancer type was 0.21

UVA is mutagenic for the skin [26], and numerous observational studies have reported an increased risk of skin cancers in PUVA-treated psoriasis patients, including KCs and melanoma [11, 27, 28]. Clinical studies also indicate an increased risk of melanoma and KCs among patients treated with PUVA compared with the general population [11, 29]. Orally-ingested furocoumarins are well absorbed in the gastrointestinal tract and quickly transported in blood to numerous tissues including the skin [30, 31], with a concentration peak in these tissues at 2–4 h after consumption [32]. In the blood, furocoumarins can be distributed into multiple tissue types and allow DNA replication with damage, leading to carcinogenesis and the formation of skin tumors at high doses [33]. While DNA is the major target for psoralen action, leading to the stimulation of skin cell proliferation, psolarens may also bind to other specific and high-affinity sites in mammalian cells, which may modulate

furocoumarin-induced phototoxicity [34]. Thus, a positive association between citrus intake and skin cancer risk that is heightened by UV exposure, as suggested by findings from the NHS, HPFS, WHI and this cohort, is highly plausible. Another hypothesis to explain the positive association between citrus fruit and melanoma risk is related to the potential contamination of citrus by pesticides. Previous research reported the presence of various pesticides in citrus fruits [35] and a positive association between several pesticides and melanoma risk [36].

Nevertheless, citrus products are also known to have antioxidant effects that could protect DNA against oxidative damage, regulate cell growth, and induce apoptosis [37]. They are also a significant source of vitamin C, and vitamin C-rich foods were suggested to protect against cancer risk [38]. Moreover, while citrus intake was positively associated with skin cancer risk in our study, citrus intakes

Table 5 Hazard ratios (HRs) and 95% confidence intervals (CIs) for intake of citrus juice and risk of skin cancer, EPIC cohort (n = 270,112)

	Citrus juice intake				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend
N	67,364	67,692	67,268	67,788	
Mean (g/day)	0.01	2.8	17.6	117.7	
Skin cancer					
No cases	2089	1725	2154	2480	
Age-adjusted HR (95% CI)	1 (ref)	1.03 (0.96–1.10)	1.10 (1.03–1.17)	1.16 (1.09–1.23)	< 0.0001
Multivariable-adjusted HR[a] (95% CI)	1 (ref)	0.99 (0.93–1.06)	1.04 (0.98–1.12)	1.09 (1.02–1.16)	0.002
Multivariable-adjusted HR[b] (95% CI)	1 (ref)	0.99 (0.92–1.06)	1.04 (0.97–1.11)	1.08 (1.02–1.16)	0.004
Melanoma					
No cases	395	255	349	372	
Age-adjusted HR (95% CI)	1 (ref)	1.04 (0.87–1.23)	1.07 (0.92–1.26)	0.96 (0.83–1.12)	0.64
Multivariable-adjusted HR[a] (95% CI)	1 (ref)	1.01 (0.85–1.20)	1.03 (0.88–1.21)	0.92 (0.79–1.07)	0.30
Multivariable-adjusted HR[b] (95% CI)	1 (ref)	1.01 (0.84–1.21)	1.03 (0.87–1.22)	0.92 (0.78–1.08)	0.31
BCC					
No cases	1244	1225	1501	1634	
Age-adjusted HR (95% CI)	1 (ref)	1.03 (0.95–1.12)	1.10 (1.02–1.20)	1.19 (1.10–1.29)	< 0.0001
Multivariable-adjusted HR[a] (95% CI)	1 (ref)	0.99 (0.91–1.07)	1.04 (0.96–1.13)	1.11 (1.02–1.20)	0.004
Multivariable-adjusted HR[b] (95% CI)	1 (ref)	0.99 (0.91–1.07)	1.04 (0.95–1.13)	1.10 (1.01–1.19)	0.008
SCC					
No cases	362	179	237	387	
Age-adjusted HR (95% CI)	1 (ref)	1.01 (0.84–1.22)	1.20 (1.00–1.43)	1.29 (1.11–1.50)	0.0004
Multivariable-adjusted HR[a] (95% CI)	1 (ref)	0.98 (0.81–1.19)	1.16 (0.97–1.39)	1.25 (1.07–1.46)	0.001
Multivariable-adjusted HR[b] (95% CI)	1 (ref)	0.95 (0.78–1.16)	1.11 (0.92–1.35)	1.23 (1.05–1.44)	0.004

Age-adjusted: adjusted for age and stratified by study center, sex, and age at recruitment

BCC basal-cell carcinoma, *CI* confidence intervals, *EPIC* European Prospective Investigation into Cancer and Nutrition, *HR* hazard ratio, *SCC* squamous-cell carcinoma

[a]Stratified by study center, sex, age at recruitment, and adjusted for education (none, primary school, technical/professional school, secondary school, university or higher degree), body mass index (BMI; < 25, 25–29, or ≥ 30 kg/m^2), smoking (never, former, and current), alcohol intake (non-consumer, then categorized in quartiles, g per day), physical activity (metabolic equivalent of task [MET] hour/week), and energy intake (continuous)

[b]Additionally adjusted for total vegetable intake (tertiles), citrus fruit (tertiles), non-citrus juice (tertiles) and coffee intake (tertiles). $P_{homogeneity}$ for citrus juice and skin cancer type was 0.02

were inversely associated with non-skin cancers (lung [39], gastric [29, 30], prostate [40], and thyroid cancers [41]) in EPIC. However, citrus consumption was not associated with the risk of major non-skin cancers (breast, prostate, lung, and colorectal cancers) in the NHS/HPFS cohorts [1, 2].

In our study, when participants from centers with no available data on citrus juice intake were included back in the analysis, we no longer observed an association between citrus fruit and melanoma, although associations remained for other outcomes. Patterns of citrus fruit consumption differ across European countries, and it is possible that melanoma risk is more strongly associated with some types of citrus fruit, as suggested by the NHS/HPFS analyses in which associations were restricted to grapefruit [1, 2]. It could be hypothesized that grapefruit consumption was less frequent in these centers. In addition, the processes undertaken by the agricultural and food industries, which may differ across European countries, may also influence furocoumarin contents in citrus [31, 42, 43]. However, since data on type of citrus fruit were not available, we were unable to clarify the origin of this divergent result. Additional research is requested in different countries with detailed data on type of citrus fruit and juice to increase our understanding of these associations.

The main limitation of our study was the lack of information on recreational UV exposure; we cannot rule out residual confounding by this factor, since stratification by study center or adjustment for outdoor recreational physical activity may not have sufficiently attenuated this limitation. In addition, we lacked data on other skin cancer risk factors, such as pigmentary traits or family history of skin cancer. Moreover, combining data from different centers increased statistical power, but also may have resulted in heterogeneity because of differences in study population characteristics.

However, we found no evidence for heterogeneity across countries for these associations. Furthermore, information on type of citrus was not available in EPIC; therefore we were not able to examine associations by citrus type. However, exposure to furanocoumarins in a Western diet was reported to primarily come from grapefruit juice [44], and grapefruit and orange juice intakes showed the strongest associations with melanoma, BCC, and SCC risks in the NHS and HPFS. In addition, dietary intakes and confounding factors were self-reported and some degree of misclassification cannot be excluded. However, such misclassification is likely to be non-differential, which would most likely result in an underestimation of the associations. In EPIC, diet was evaluated through a single dietary assessment at recruitment, which did not allow to take into account potential dietary changes during follow-up. Also, while skin cancer cases were ascertained with high confirmation rates, KCs are often not systematically recorded in cancer registries; thus, underestimation of the incidence of these cancers in some centers is likely. Despite these limitations, our study has several strengths, including its prospective design, particularly large study population and long duration of follow-up, and the fact that it spans a large number of European countries with a high variety of dietary profiles. In addition, dietary intake was assessed using validated dietary questionnaires in all centers.

In conclusion, our findings suggest modest positive linear relationships between citrus intake and skin cancer risk, which were mostly driven by associations with BCC and SCC. While high citrus fruit intakes were associated with melanoma risk, citrus juice intake was positively and linearly associated with BCC and SCC risks. Although additional studies are needed because of limited data on UV exposure and type of citrus fruit and juice in this analysis, the current findings lend support to previous research. Further studies with biomarker data, availability of detailed data on type of citrus, and the ability to examine UV exposure behaviors are warranted to clarify these associations and to examine the phototoxicity mechanisms of furocoumarin-rich foods.

Compliance with ethical standards

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