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Dietary β-carotene, vitamin C and E intake and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC)

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Abstract So far, studies on dietary antioxidant intake, including β-carotene, vitamin C and vitamin E, and breast cancer risk are inconclusive. Thus, we addressed this question in the European Prospective Investigation into Cancer and Nutrition. During a median follow-up time of 8.8 years, 7,502 primary invasive breast cancer cases were identified. Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). All analyses were run stratified by menopausal status at recruitment and, additionally, by smoking status, alcohol intake, use of exogenous hormones and use of dietary supplements. In the multivariate analyses, dietary intake of β-carotene, vitamin C and E was not associated with breast cancer risk in premenopausal [highest vs. lowest quintile: HR, 1.04 (95% CI, 0.85–1.27), 1.12 (0.92–1.36) and 1.11 (0.84–1.46), respectively] and postmenopausal women

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[0.93 (0.82–1.04), 0.98 (0.87–1.11) and 0.92 (0.77–1.11), respectively]. However, in postmenopausal women using exogenous hormones, high intake of β-carotene [highest vs. lowest quintile; HR 0.79 (95% CI, 0.66–0.96), P_{trend} 0.06] and vitamin C [0.88 (0.72–1.07), P_{trend} 0.05] was associated with reduced breast cancer risk. In addition, dietary β-carotene was associated with a decreased risk in postmenopausal women with high alcohol intake. Overall, dietary intake of β-carotene, vitamin C and E was not related to breast cancer risk in neither pre- nor postmenopausal women. However, in subgroups of postmenopausal women, a weak protective effect between β-carotene and vitamin E from food and breast cancer risk cannot be excluded.

Keywords β-Carotene · Vitamin C · Vitamin E · Breast cancer · Diet · EPIC

Introduction

The role of antioxidants in the aetiology of breast cancer is still unclear [1–3, 17]. In an early analysis of the EPIC-cohort, no association between fruit and vegetable intake and breast cancer risk was found [4]. However, it is biologically plausible that diets high in antioxidants protect against cancer. Dietary antioxidants such as carotenoids, vitamins C and E can neutralise free radicals and may protect DNA from oxidative damage [5, 6]. In order to account for huge differences in antioxidant content of the variety of fruit and vegetables, it is worthwhile to perform studies at the nutrient level, i.e. to test for the association between dietary antioxidant intake (derived from food consumption data) and cancer risk. However, it is acknowledged that interpretation of the results in terms of dietary intake recommendations shall be done at the food level again.

Findings from epidemiologic studies on dietary intake of carotenoids (with pro-vitamin-A activity) and retinol, as biologically active metabolite, and breast cancer risk have been inconclusive [3]. Mostly, the results of cohort studies showed no statistically significant association between β-carotene intake and breast cancer risk [7–10]. In contrast, in one cohort study (the Nurses Health Study), a significantly inverse association between β-carotene intake and breast cancer risk has been observed in premenopausal but not in postmenopausal women [11]. In addition, β-carotene supplementation did not affect cancer incidence in women [12]. Most prospective studies showed no association between vitamin C intake and breast cancer risk [9, 13–15]. However, in a meta-analysis of nine case-control studies on vitamin C intake and breast cancer, an inverse association has been reported [16]. Another meta-analysis reported reduced breast cancer risk for higher dietary β-carotene and

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vitamin C levels [17]. Further investigation of biomarkers of antioxidants did not clarify the relationships [18–21].

Previous work indicates a modest protective effect of antioxidants in populations with potentially higher oxidative stress [11, 22]: high intakes of vitamin C and E in premenopausal female smokers were associated with lower breast cancer risk [22]. Also, an inverse association between β-carotene and breast cancer risk in premenopausal women consuming $\geq$15 g/day alcohol was reported [11]. In addition, there is evidence from a gene–environment study that oxidative stress is involved in the association between hormone therapy and breast cancer risk in postmenopausal women [23].

The objectives of our study were to explore the associations between dietary intake of β-carotene, vitamin C and vitamin E and breast cancer risk by menopausal status and to investigate subgroups with potentially higher oxidative stress.

Methods

Study population

European Prospective Investigation into Cancer and Nutrition (EPIC) is a multicentre prospective cohort study designed to primarily investigate the associations of diet and lifestyle factors with the incidence of cancer. Between 1992 and 2000, approximately 520,000 individuals were recruited in 23 research centres in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom (UK). The study design is described in detail elsewhere [24, 25]. In brief, most study subjects were recruited from the general population in a given geographical area. Eligible subjects were invited to participate in the studies, and those

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who accepted gave informed consent and completed questionnaires on their diet, lifestyle and medical history. The French EPIC cohort (based on female members of the health insurance for state school employees), part of the Oxford cohort, UK (based on vegetarians and healthy eaters), the Utrecht cohort, the Netherlands and the Florence cohort, Italy (both based on women attending breast cancer screening), the Ragusa cohort, Italy and most of the Spanish cohorts (both based on blood donors and their spouses) are not based on a random selection of the underlying population.

The EPIC-cohort consists of 345,995 women mostly aged between 35 and 70 years of which participants were excluded due to missing nondietary data or due to not filling in the dietary questionnaire or due to being in the top or bottom 1% ratio of the energy intake and energy requirement ($N = 10,127$). We further excluded women due to missing values reporting on breast cancer occurrence or non-invasive breast cancer or missing information on behaviour of the tumour ($N = 1,375$) resulting in 334,493 women including 7,502 cases with invasive breast cancer. The analytic cohort with full set of covariates comprised 288,776 women including 6,478 cases of invasive breast cancer covering in total 2,518,722 person-years.

Diet

Habitual diet over the previous 12 months was measured by country-specific validated questionnaires designed to capture local dietary habits as previously described in detail [24, 26]. In Greece, Spain and Ragusa, a face-to-face dietary interview was performed. Questionnaires in France, Northern Italy, Spain, the Netherlands and Greece were quantitative, estimating individual average portion sizes systematically. Those in Denmark, Germany, Norway, Naples in Italy and Umea in Sweden were semiquantitative, with the same standard portion assigned to all subjects. In Malmö and in the United Kingdom, the dietary questionnaire was combined with food records. Rough data on the supplementation of vitamin or multivitamin preparations in general (yes, no) were collected by dietary questionnaire for about 80% of the cohort. The algorithm by which women were allocated to menopausal status at enrolment has been described in detail before [27]. In brief, information on menstrual history, type of menopause (natural, surgical), use of oral contraceptives and menopausal hormones has been used to classify women according to menopausal status at enrolment.

Covariates

Height and weight were measured in all EPIC centres except in France, Norway and Oxford, for which self-rated

anthropometric measures were assessed by questionnaires. Extensive, standardised information about medical history including medication and reproductive history, physical activity, smoking, alcohol consumption, and other lifestyle factors was collected by a separate questionnaire.

Endpoint

Cases of cancer occurring after recruitment are identified through local and national cancer registries in seven of the ten countries (Denmark, Italy, Norway, Spain, Sweden, the Netherlands and United Kingdom). Data on mortality were also obtained from either cancer registries or mortality registries. In France, Germany and Greece, active follow-up was carried out applying a combination of contacts with national health insurances and/or active follow-up through the study subjects or their next-of-kin. In all EPIC centres, cancer diagnosis was confirmed by review of pathology reports. We used the Tenth Revision International Classification of Diseases, Injury and Causes of Death (ICD-10), and invasive breast cancer was defined as C50.0–50.9.

Statistical analysis

We calculated the number of person-years for each person under observation. Participants were censored as follows: December 1999 (Turin), June 2000 (Bilthoven), December 2000 (Asturias, Murcia, Cambridge), December 2001 (Florence, Varese, Ragusa, Granada, Navarra, San Sebastian, Oxford, Malmo, Norway), June 2002 (France), December 2002 (Umea, Aarhus, Copenhagen, Naples) and June 2003 (Utrecht). For Germany and Greece, the end of the follow-up was considered to be the last-known contact, the date of diagnosis or the date of death, whichever came first. We used Cox proportional hazard method to estimate the hazard ratio (HR) and 95% confidence intervals (CI) of each quintile compared to the lowest quintile of antioxidant intake. The age at recruitment was used as entry time or t0, and exit time or t1 was the age at breast cancer incidence or censoring. The variable centre was used as stratum in order to control for differences in the questionnaire design and follow-up procedures.

Dietary intake of β-carotene, vitamin C and vitamin E were estimated from dietary questionnaires, calculated based on country-specific food composition tables and expressed as mg/day. The nutrient intake levels were analysed using variables as categorical, by EPIC-wide quintiles or as continuous (β-carotene per 2 mg/day, vitamin C per 100 mg/day and vitamin E per 10 mg/day) in the so-called 'observed' models.

All multivariate models were controlled for estimated energy from protein and carbohydrates (kcal/day, continuous), saturated fatty acids (SFA, g/day, continuous), monounsaturated fatty acids (MUFA, g/day, continuous), polyunsaturated fatty acids (PUFA, g/day, continuous), alcohol intake (g/day, continuous), weight (kg, continuous), height (m, continuous), age at menarche ($\leq$12, 13–14, $\geq$15 years), parity (yes/no), age at first full-term pregnancy (nulliparous, <20, 20–30, >30 years), use of hormone therapy at recruitment (yes, no, missing), smoking status (current, former, never, unknown), overall physical activity [metabolic equivalent of energy expenditure score (MET) classified as inactive, moderately inactive, moderately active, active] [28] and education (none, primary school, technical/professional school, secondary school, university). All models were calculated stratified by menopausal status at recruitment (pre-, peri-, postmenopausal as defined in [13]). In addition, stratified analyses were run by smoking status, alcohol consumption levels, the use of exogenous hormones and the use of supplementary vitamins. Heterogeneity between centres ($P_{\text{heterogeneity}}$) of effect was tested using Wald statistics [29].The median values for antioxidants within each quintile was entered in a regression model, and the significance was tested by the Wald's test (P_{trend}). Interaction was investigated by including a cross-product term in the equation, and P for interaction was calculated with the log-likelihood test. ($P_{\text{interaction}}$). Two-sided P-values are reported. All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Calibration

To correct for systematic over- or underreporting, dietary intakes were calibrated by means of data obtained from a detailed computerised 24-h diet recall (24HR) as second dietary assessment in a random sample of the cohort ($N = 21,522$ women in the present study) [30]. Country-specific calibration models were used to predict dietary exposures for all participants [31]. The 24HR values were regressed on the intake values for β-carotene, vitamin C, vitamin E, SFA, MUFA, PUFA, alcohol and energy from carbohydrates and proteins. Disease models were then run with the calibrated value of the nutrient of interest applying also the calibrated values of the adjustment variables.

Results

The number of breast cancer cases by country and age at diagnosis is shown in Table 1. During median follow-up time of 8.8 years, 7,502 cases with invasive breast cancer occurred. The median intake of β-carotene ranged between 1.6 mg/day in Spain and 4.5 mg/day in Greece and for vitamin C between 80 mg/day in Norway and 201 mg/day in Greece. Median intake of vitamin E was lowest in

Table 1 Description of the EPIC-cohort with 7,502 primary incident invasive breast cancer cases during 2,943,465 person years

	Breast cancer cases	Person-years (PY)	β-Carotene intake median (mg/day)	Vitamin C intake median (mg/day)	Vitamin E intake median (mg/day)
Country					
France	2,459	735,560	3.70	130.70	13.33
Italy	677	256,901	2.46	132.82	7.89
Spain	319	241,081	1.60	136.57	7.93
United Kingdom	935	441,049	3.19	133.74	13.14
The Netherlands	569	228,570	2.37	111.08	8.98
Greece	114	108,442	4.48	200.82	8.74
Germany	457	227,017	2.34	105.42	10.17
Sweden	680	270,520	2.61	95.88	7.28
Denmark	824	215,742	4.05	97.64	8.15
Norway	468	210,276	2.69	80.11	7.68
Age band (age at diagnosis)					
<40	66	97,904			
40–49	985	345,022			
50–59	3,357	969,541			
60–69	2,520	1,024,265			
≥70	574	498,426			

Study centres per country, France: North-East of France, North-West of France, South of France, South coast of France; Italy: Florence, Varese, Ragusa, Turin, Naples; Spain: Asturias, Granada, Murcia, Navarra, San Sebastian; United Kingdom: Cambridge, Oxford Health conscious, Oxford General population; the Netherlands: Bilthoven, Utrecht; Germany: Heidelberg, Potsdam; Sweden: Malmö, Umea; Denmark: Aarhus, Copenhagen; Greece: Athens; Norway: Tromso

Sweden (7.28 mg/day) and highest in France (13.33 mg/day). Basic characteristics of women according to consumption levels of antioxidants are shown in Table 2. In comparison with the low consumption category (Q1), women with higher intakes of antioxidants (Q5), smoked currently less, were more physically active, drank more alcohol and reported higher levels of education.

Table 3 shows hazard ratios and 95% confidence intervals for the risk of breast cancer by dietary β-carotene, vitamin C and vitamin E intake among **premenopausal women**. Consistently for different exposure models, dietary β-carotene and vitamin C intake from food was not associated with breast cancer risk. For vitamin E intake, the trend test indicated a positive association with breast cancer risk in premenopausal women overall and in subgroups with moderate alcohol consumption and no use of supplements. Further adjustment for dietary supplement use did not substantially affect the estimates (please see supplementary Tables 2, 3). Alcohol intake did not modify the association between antioxidants and breast cancer risk in premenopausal women.

In Table 4, hazard ratios and 95% confidence intervals for the risk of breast cancer by dietary β-carotene, vitamin C and vitamin E intake among **postmenopausal women** are shown. Overall, also in postmenopausal women, no associations were found for dietary intake of β-carotene (highest vs. lowest quintile: HR, 0.93; 95% CI (0.82–1.04);

$P_{\text{heterogeneity}} = 0.093$), vitamin C [0.98 (0.87–1.10); $P_{\text{heterogeneity}} = 0.065$] and vitamin E [0.92 (0.77–1.11); $P_{\text{heterogeneity}} = 0.029$]. Exclusion of Norway and Italy in order to increase homogeneity between centres did not substantially influence the estimates for vitamin E intake [0.92 (0.75–1.12); $P_{\text{heterogeneity}} = 0.226$]. Neither adjustment for supplementary vitamin use did influence the estimates nor do the results of a sub-analysis in non-users indicate effect modification by supplement use (supplementary Tables 1, 2). No substantial differences in the risk estimates emerged by exclusion of breast cancer cases diagnosed within the first 2 years of follow-up in order to explore whether cancers diagnosed closely to recruitment date influenced the findings. When analysing all perimenopausal women ($N = 62,808$), no relationship between β-carotene, vitamin E and vitamin C emerged (data not shown).

Stratification for the use of exogenous hormones, revealed that among postmenopausal women using exogenous hormones, high intake of β-carotene when compared to low intake was related to lower breast cancer risk [0.79 (0.66–0.96); $P_{\text{trend}} = 0.06$]. High vitamin C intake was also associated with lower breast cancer risk [0.88 (0.72–1.07)], but reached statistical significance in the continuous model with observed intake data [0.989 (0.979–0.999); $P_{\text{trend}} = 0.05$]. For vitamin E, no association was found. Only the interaction between exogenous hormone use and vitamin C intake was statistically

Table 2 Distribution of breast cancer risk factors in the extreme quintiles of dietary intake of β-carotene, vitamins C and E among women in the EPIC-cohort

	β-Carotene (mg/d)		Vitamin C (mg/d)		Vitamin E (mg/d)	
	Q1 Mean (SD)	Q5 Mean (SD)	Q1 Mean (SD)	Q5 Mean (SD)	Q1 Mean (SD)	Q5 Mean (SD)
Dietary intake	1.20 (0.35)	7.28 (3.72)	56.3 (14.3)	237.7 (67.8)	5.4 (1.0)	19.5 (4.8)
Continuous covariates						
Age (year)	49.5 (9.9)	52.4 (9.5)	50.4 (9.1)	50.8 (10.5)	51.6 (9.0)	50.0 (10.3)
Saturated fatty acids (g/day)	25.92 (10.49)	31.47 (12.55)	26.95 (10.68)	31.37 (12.82)	22.55 (8.17)	35.33 (13.30)
Monounsaturated fatty acids (g/day)	24.41 (9.78)	31.90 (15.18)	23.01 (8.55)	35.06 (15.74)	21.71 (8.59)	33.52 (12.36)
Polyunsaturated fatty acids (g/day)	10.99 (4.99)	15.79 (7.08)	11.20 (4.85)	15.75 (7.11)	8.05 (2.66)	21.34 (6.21)
Energy from protein and carbohydrates (kcal/day)	1,035.03 (295.08)	1,298.32 (353.99)	985.54 (272.76)	1,370.15 (370.12)	937.87 (244.02)	1,398.46 (360.12)
Alcohol consumption (g/day) median	2.5	3.7	2.8	3.1	1.9	4.8
Height (m)	161.7 (7.0)	162.2 (6.5)	163.1 (6.6)	161.3 (6.8)	161.7 (7.0)	162.6 (6.4)
Weight (kg)	66.4 (11.7)	65.8 (11.8)	66.0 (11.9)	66.1 (11.8)	66.7 (11.7)	64.3 (11.4)
Categorial covariates	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Menarche ≤12 years	19,328 (35.3)	20,263 (36.0)	17,485 (32.3)	22,944 (39.6)	18,254 (34.4)	21,658 (38.9)
Parous women	45,767 (83.6)	48,195 (85.5)	46,820 (86.6)	48,395 (83.4)	46,710 (87.7)	46,304 (83.1)
Postmenopausal at recruitment	22,606 (41.3)	28,742 (51.0)	23,872 (44.1)	25,596 (44.1)	26,249 (49.3)	22,574 (40.5)
Hormone therapy (HT) users	11,590 (21.2)	12,701 (22.5)	12,993 (24.0)	11,076 (19.1)	10,119 (19.0)	13,499 (24.2)
Current smokers	14,593 (26.7)	9,181 (16.3)	16,126 (29.8)	86,24 (14.9)	14,394 (27.0)	7,009 (12.6)
Physically active	3,972 (7.3)	5,265 (9.3)	3,138 (5.8)	64,42 (11.1)	3,521 (6.6)	4,900 (8.8)
≥Secondary school	18,842 (34.3)	28,951 (49.7)	20,045 (37.1)	29,824 (51.4)	18,381 (34.5)	33,266 (59.7)

significant [$P_{interaction} = 0.016$]. Figure 1a–d shows the combined and country-specific HRs for postmenopausal breast cancer risk in relation to β-carotene and vitamin C intake and exogenous hormone use. Since the number of cases is relatively low in Greece and Norway and the follow-up time is short, these results should be interpreted with caution.

Stratification by levels of alcohol consumption revealed an inverse association between breast cancer risk and dietary β-carotene intake among women with high ($\geq$10 g/day) alcohol consumption [0.75 (0.62–0.92)]. For vitamin C and E intake, no clear associations were found. None of the interactions with alcohol consumption was statistically significant (β-carotene $P_{interaction} = 0.967$, vitamin C $P_{interaction} = 0.875$ and vitamin E $P_{interaction} = 0.894$).

Stratification by smoking status (supplementary Table 1) revealed to none of the subgroups a remarkable association between the intake of β-carotene, vitamin C and E from food and breast cancer risk, except for associations of higher vitamin C with higher breast cancer risk in former and never smokers among premenopausal women and increasing vitamin E and breast cancer risk in current smokers among postmenopausal women. Overall, none of the interaction terms between antioxidant intake and smoking status was statistically significant (β-carotene

$P_{interaction} = 0.446$, vitamin C $P_{interaction} = 0.582$ and vitamin E $P_{interaction} = 0.346$).

Discussion

In this large prospective study, no consistent relationships between dietary intake of β-carotene, vitamins C or E and breast cancer risk were found among pre- and postmenopausal women. Also in perimenopausal women, no association was found (data not shown). However, in subgroup analyses, we found some evidence of an association between β-carotene and vitamin C intake and lower breast cancer risk among postmenopausal women using hormones. A lower risk was also observed for high β-carotene intake among postmenopausal women consuming more than 10 g alcohol per day. In premenopausal women, vitamin E intake from food was in trend positively associated with breast cancer risk.

Our results are in agreement with former research [1, 3, 7–11, 13] showing no association between β-carotene, vitamin C and E intake and breast cancer risk. However, one cohort study reported a weak protective effect of dietary β-carotene on breast cancer risk in premenopausal women [11]. Discrepancies in the associations between

Table 3 Hazard ratios and 95% confidence intervals for the risk of invasive breast cancer by dietary β-carotene, vitamin C and E intake among 116,957 premenopausal women in the EPIC-cohort

| | Quintiles | | | | | P for trend | Observed[b] | Calibrated[b] | Heterogeneity by centre |
	Q1 HR (95% CI)	Q2 HR (95% CI)	Q3 HR (95% CI)	Q4 HR (95% CI)	Q5 HR (95% CI)		Continuous	Continuous	
β-carotene (mg/day)									
Invasive cancers cases[a]	268	320	330	292	270				
	1	1.02 (0.86–1.20)	1.06 (0.89–1.26)	0.92 (0.76–1.10)	1.04 (0.85–1.27)	0.945	0.993 (0.942–1.048)	1.025 (0.920–1.142)	0.532
Alcohol intake ≤10 g/day[c]	188	228	214	180	188				
	1	1.09 (0.89–1.33)	1.00 (0.81–1.23)	0.80 (0.64–1.01)	0.99 (0.78–1.26)	0.585	0.976 (0.910–1.046)	0.974 (0.855–1.109)	0.259
$P_{interaction}$ 0.4146									
Alcohol intake >10 g/day[c]	80	92	116	112	82				
	1	0.90 (0.66–1.24)	1.20 (0.88 –1.64)	1.22 (0.88–1.68)	1.15 (0.80–1.65)	0.287	1.030 (0.946–1.112)	1.116 (0.914–1.362)	0.719
No supplements[a]	146	186	193	167	135				
	1	1.06 (0.85–1.33)	1.14 (0.90–1.44)	0.96 (0.75–1.23)	1.08 (0.82–1.43)	0.798	0.995 (0.913–1.085)	1.042 (0.906–1.200)	0.839
$P_{interaction}$ 0.0381									
Vitamin C (mg/day)									
Invasive cancer cases[a]	239	294	337	304	306				
	1	1.06 (0.89–1.27)	1.17 (0.99–1.40)	1.07 (0.89 –1.28)	1.12 (0.92–1.36)	0.370	1.003 (0.994–1.012)	1.074 (0.865–1.333)	0.239
Alcohol intake ≤10 g/day[c]	172	189	230	190	217				
	1	0.99 (0.80–1.22)	1.13 (0.92–1.40)	0.91 (0.73–1.14)	1.04 (0.82–1.32)	0.919	0.999 (0.988–1.010)	0.997 (0.770–1.290)	0.551
$P_{interaction}$ 0.9937									
Alcohol intake >10 g/day[c]	67	105	107	114	89				
	1	1.27 (0.93–1.74)	1.26 (0.91–1.73)	1.45 (1.04–2.01)	1.30 (0.91–1.86)	0.329	1.011 (0.995–1.027)	1.160 (0.796–1.691)	0.329
No supplements[a]	105	168	209	184	161				
	1	1.16 (0.91–1.49)	1.32 (1.04–1.68)	1.17 (0.91–1.51)	1.15 (0.88–1.51)	0.690	1.004 (0.992–1.016)	1.163 (0.819–1.650)	0.986
$P_{interaction}$ 0.0709									
Vitamin E (mg/day)									
Invasive cancer cases[a]	222	268	286	329	375				
	1	1.00 (0.83–1.21)	1.00 (0.82– 1.22)	1.04 (0.83–1.29)	1.11 (0.84–1.46)	0.014	0.925 (0.745–1.150)	1.154 (0.644–2.070)	0.135
Alcohol intake ≤10 g/day[c]	158	181	194	216	249				
	1	0.98 (0.79–1.23)	1.00 (0.79–1.17)	1.04 (0.80–1.35)	1.15 (0.82–1.61)	0.020	0.963 (0.744–1.245)	1.020 (0.501–2.077)	0.647
$P_{interaction}$ 0.8570									
Alcohol intake >10 g/day[c]	64	87	92	113	126				
	1	1.07 (0.76–1.51)	1.05 (0.72–1.52)	1.10 (0.73–1.66)	1.03 (0.61–1.74)	0.765	0.794 (0.525–1.200)	0.611 (0.241–1.551)	0.804
No supplements[a]	114	145	155	182	231				
	1	1.07 (0.82–1.38)	1.06 (0.80–1.40)	1.12 (0.82–1.52)	1.32 (0.90–1.94)	0.007	0.951 (0.699–1.292)	1.105 (0.508–2.404)	0.773
$P_{interaction}$ 0.1039									

[a] Stratified by centre and age in 1-year intervals and adjusted for: energy from protein and carbohydrates (kcal/day, continuous), saturated fatty acid (g/day; continuous), polyunsaturated fatty acids (g/day; continuous), alcohol intake (g/day, continuous), monounsaturated fatty acids (g/day; continuous), height (kg, continuous), weight (kg, continuous), age at menarche (≤12, 13–14, ≥15 years), parity (yes/no), age at first full-term pregnancy (<20, 20–30, >30, nulliparous), use of hormone therapy at recruitment (yes/no), smoking status (current, former, never), physical activity index (inactive, moderately inactive, moderately active, active) education (none, primary school, technical/professional school, secondary school, university)

[b] Increments: β-carotene 2 mg/day, vitamin C 10 mg/day and vitamin E 10 mg/day

[c] Stratified by centre and age in 1-year intervals and adjusted according to the [a] except for alcohol intake (g/day, continuous)

Table 4 Hazard ratios and 95% confidence intervals for the risk of invasive breast cancer by dietary β-carotene, vitamin C and vitamin E intake among 154,012 postmenopausal women in the EPIC-cohort

	Quintiles					P for trend	Observed[b]	Calibrated[b]	Heterogeneity by centre
	Q1 HR (95% CI)	Q2 HR (95% CI)	Q3 HR (95% CI)	Q4 HR (95% CI)	Q5 HR (95% CI)		Continuous	Continuous	
β-Carotene (mg/day)									
Invasive cancer cases[a]	612	619	745	767	863				
	1	0.93 (0.83–1.04)	0.99 (0.89–1.11)	0.95 (0.85–1.07)	0.93 (0.82–1.04)	0.292	0.982 (0.958–1.007)	0.979 (0.924–1.038)	0.093
Current hormone use: yes[d]	237	250	282	316	362				
	1	0.87 (0.72–1.04)	0.86 (0.71–1.03)	0.85 (0.71–1.03)	0.79 (0.66–0.96)	0.060	0.971 (0.935–1.008)	0.970 (0.902–1.044)	0.574
$P_{interaction}$ 0.3189									
Alcohol intake ≤10 g/day[c]	388	401	497	507	564				
	1	0.99 (0.86–1.15)	1.09 (0.95–1.26)	1.06 (0.92–1.20)	1.04 (0.90–1.20)	0.469	0.992 (0.962–1.024)	1.017 (0.945–1.094)	0.041
$P_{interaction}$ 0.9672									
Alcohol intake >10 g/day[c]	224	218	248	260	299				
	1	0.79 (0.65–0.96)	0.81 (0.67–0.99)	0.78 (0.64–0.95)	0.75 (0.62–0.92)	0.159	0.970 (0.931–1.011)	0.956 (0.872–1.048)	0.243
No supplements[a]	288	290	401	398	360				
	1	0.89 (0.75–1.05)	1.07 (0.91–1.26)	0.98 (0.83–1.16)	0.92 (0.77–1.10)	0.674	0.975 (0.931–1.021)	0.968 (0.855–1.096)	0.096
$P_{interaction}$ 0.1957									
Vitamin C (mg/day)									
Invasive cancer cases[a]	690	666	760	787	703				
	1	0.91 (0.82–1.02)	0.99 (0.88–1.10)	1.01 (0.91–1.13)	0.98 (0.87–1.11)	0.794	1.000 (0.994–1.006)	1.091 (0.952–1.251)	0.065
Current hormone use: yes[d]	289	315	294	290	250				
	1	1.01 (0.86–1.19)	0.92 (0.78–1.10)	0.92 (0.76–1.10)	0.88 (0.72–1.07)	0.053	0.989 (0.979–0.999)	0.856 (0.678–1.081)	0.387
$P_{interaction}$ 0.0161									
Alcohol intake ≤10 g/day[c]	449	424	501	499	484				
	1	0.89 (0.78–1.02)	1.00 (0.87–1.14)	0.97 (0.85–1.12)	0.98 (0.84–1.14)	0.818	1.001 (0.994–1.008)	1.165 (0.988–1.374)	0.424
$P_{interaction}$ 0.8750									
Alcohol intake >10 g/day[c]	241	242	259	288	219				
	1	0.96 (0.80–1.15)	0.97 (0.81–1.17)	1.12 (0.92–1.35)	0.97 (0.78–1.10)	0.956	0.997 (0.986–1.008)	0.895 (0.706–1.135)	0.063
No supplements[a]	302	326	379	399	331				
	1	0.93 (0.79–1.09)	0.95 (0.81–1.11)	0.97 (0.83–1.15)	0.92 (0.77–1.10)	0.247	0.994 (0.986–1.003)	0.981 (0.796–1.209)	0.865
$P_{interaction}$ 0.0364									
Vitamin E (mg/day)									
Invasive cancer cases[a]	691	684	746	747	738				
	1	0.95 (0.83–1.09)	0.97 (0.83–1.12)	1.03 (0.87–1.21)	0.98 (0.79–1.23)	0.813	1.089 (0.923–1.285)	1.349 (0.878–2.073)	0.047
Current hormone use: yes[d]	244	256	295	322	330				
	1	0.92 (0.82–1.02)	0.97 (0.85–1.90)	0.96 (0.83–1.10)	0.92 (0.77–1.11)	0.301	1.065 (0.925–1.227)	1.223 (0.839–1.784)	0.029
$P_{interaction}$ 0.1277									
Alcohol intake ≤10 g/day[c]	449	449	464	497	498				
	1	0.83 (0.69–0.99)	0.85 (0.70–1.04)	0.84 (0.67–1.04)	0.83 (0.62–1.11)	0.269	0.973 (0.775–1.222)	1.237 (0.670–2.285)	0.792
$P_{interaction}$ 0.8939									

Table 4 continued

	Quintiles					P for trend	Observed[b]	Calibrated[b]	Heterogeneity by centre
	Q1 HR (95% CI)	Q2 HR (95% CI)	Q3 HR (95% CI)	Q4 HR (95% CI)	Q5 HR (95% CI)		Continuous	Continuous	
Alcohol intake >10 g/day[c]	242 / 1	235 / 0.86 (0.71–1.05)	282 / 0.97 (0.79–1.11)	250 / 0.82 (0.64–1.05)	240 / 0.82 (0.58–1.14)	0.168	1.029 (0.785–1.347)	1.078 (0.480–2.419)	0.764
No supplements[a]	314 / 1	314 / 0.92 (0.78–1.09)	337 / 0.94 (0.79–1.13)	353 / 0.92 (0.75–1.13)	419 / 0.89 (0.69–1.16)	0.090	0.985 (0.801–1.211)	1.102 (0.620–1.960)	0.307
$P_{interaction}$ 0.1574									

[a] Stratified by centre and age in 1-year intervals and adjusted for: energy from protein and carbohydrates (kcal/day, continuous), saturated fatty acids (g/day; continuous), polyunsaturated fatty acids (g/day; continuous), monounsaturated fatty acids (g/day; continuous), height (m, continuous), weight (kg; continuous), age at menarche (≤12, 13–14, ≥15 years), parity (yes/no), age at first full-term pregnancy (<20, 20–30, >30, nulliparous), use of hormone therapy at recruitment (yes/no), smoking status (current, former, never), physical activity index (inactive, moderately inactive, moderately active, active) education (none, primary school, technical/professional school, secondary school, university)

[b] Increments: β-carotene 2 mg/day, vitamin C 10 mg/day and vitamin E intake 10 mg/day

[c] Stratified by centre and age in 1-year intervals and adjusted according to [a] except for alcohol intake (g/day, continuous)

[d] Stratified by centre and age in 1-year intervals and adjusted according to [a] except for use of hormone therapy at recruitment (yes/no)

dietary antioxidants and breast cancer risk could be related to differences in the adjustment variables or the selection of subgroups and study design. Protective effects of antioxidants were predominantly found in case-control studies [16, 17], which are susceptible to recall bias. Differences in the associations could also be related to the hormone receptor status of the tumour [32–34]. Unfortunately, this information was not available for our study, nor was family history of breast cancer available for all centres. However, for some centres (France, Spain, Cambridge and Norway) with information on familiar breast cancer, a sensitivity analyses revealed no substantial differences of the risk estimates. Few studies also reported positive associations, e.g. an increased breast cancer risk has been found for obese [10] postmenopausal women with high vitamin C intake [35]. In line with our findings, vitamin E intake from foods and supplements was positively related to breast cancer risk in premenopausal women, whereas in post-menopausal women an inverse association was found [11].

Alcohol consumption leads to oxidative stress and free radical damage [36]. Stratification by levels of alcohol consumption revealed an inverse association between β-carotene intake and breast cancer risk among postmeno-pausal women who consumed more than 10 g alcohol per day. In contrast to Zhang et al. [11], we found no clear relationship among premenopausal women consuming alcohol. However, in their analyses, 15 g/day of alcohol was used as cut-point, by which we would have excluded some centres. No associations were found for vitamin C and E in alcohol consumers, independent of menopausal status.

Our finding of no apparent association between β-car-otene and breast cancer risk for smokers among both pre- and postmenopausal women is consistent with previous results concerning various carotenoids [37], although high vitamin A intake was associated with reduced breast cancer risk among premenopausal smokers in another study [22]. Between β-carotene intake and tobacco-related cancers a positive association among smokers and an inverse asso-ciation among non-smokers have been reported, but no association for non-tobacco-related cancers, including breast cancer [38]. However, our results suggest an asso-ciation of higher vitamin C with higher breast cancer risk in former and current smoker among premenopausal women, which are in line with another study [35]. In postmeno-pausal smokers, vitamin E intake was positively associated with breast cancer risk. However, since the interaction term between vitamin E intake and smoking status was not statistically significant, and no association existed after calibration of the vitamin E intake data, this result should be interpreted with caution.

Our observation of a protective association of β-caro-tene with vitamin C intake among postmenopausal current
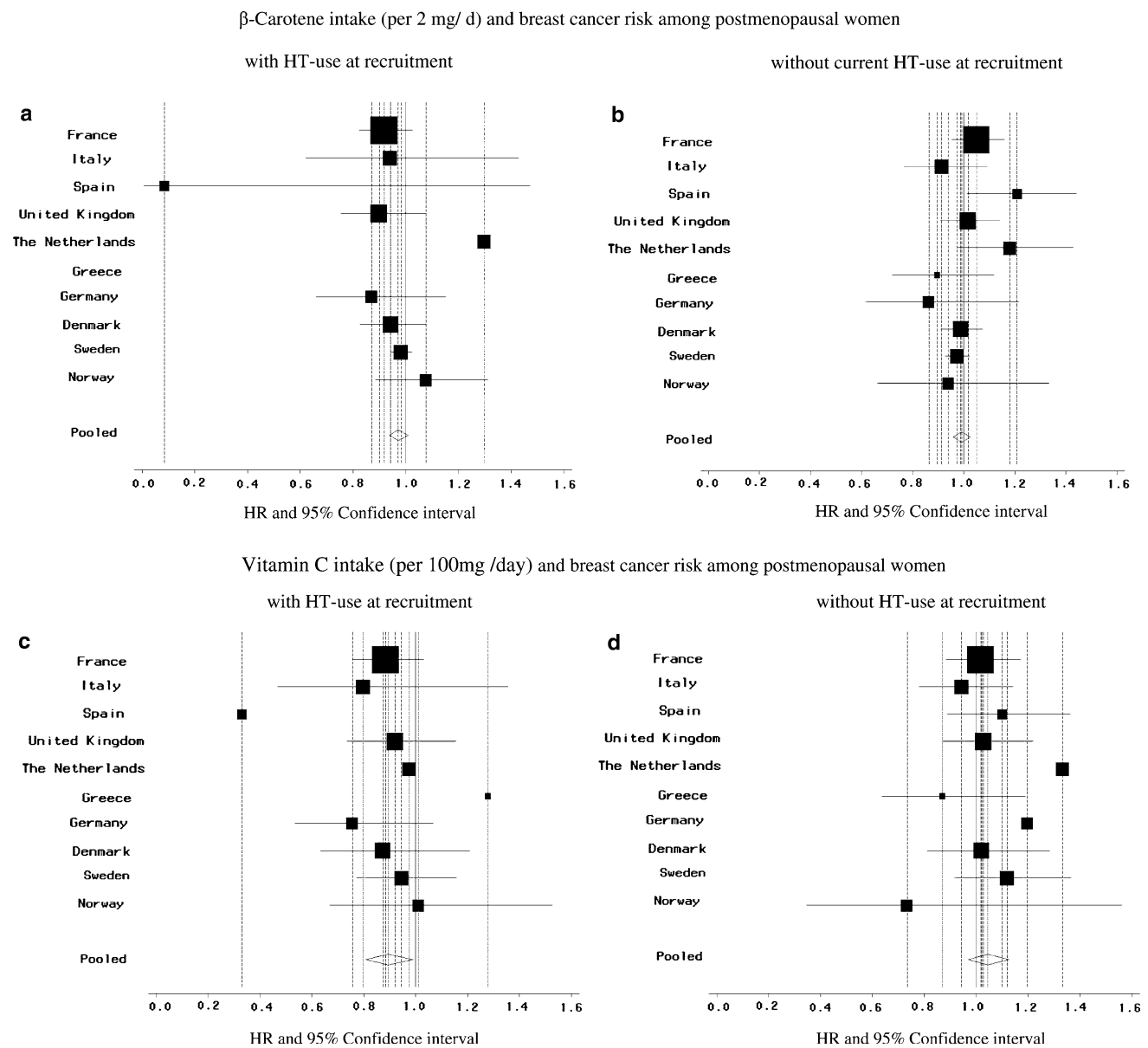
Fig. 1 Dietary intake of *β*-carotene and vitamin C (observed values) and relative risk of breast cancer (HR, 95% CI) among postmenopausal women by use of hormone therapy (HT) at recruitment and country

hormone users could also be attributed to bioactive compounds, which are highly correlated with the vitamins C and E and not yet identified or listed in common food tables. However, some support comes from in vitro studies showing a link between oestrogen-induced oxidative stress and breast cancer [39, 40]. Epidemiological studies with stratification by menopausal status and hormone therapy are scarce. However, the results of a case-control study on *β*-carotene intake suggest effect modification by HRT-use [23]. Further research including biomarker measurements is warranted to clarify the mechanisms. Given the large number of subgroups

analysed in this study, chance remains a plausible explanation of these results.

In the present study, we were interested in the effects of dietary antioxidants from foods, since users of vitamin supplements may differ from the general population [41, 42]. Previous analyses of dietary supplementation with specific dietary micronutrients showed mixed results [3], and recent results from a prospective study do not support an association between dietary multivitamin supplement use and breast cancer risk [43]. In our study, no substantial change of the risk estimates was observed by additional adjustment for supplement use (Supplementary Tables 2, 3).

Among the limitations of our study, measurement error in questionnaire-based dietary assessment has to be considered. In order to explore the exposure–disease relationship, individuals were ranked according to their intake levels, thus systematic over- or underestimation is of less relevance. In addition, models using calibrated dietary values were used to minimise measurement error. Our observations could be due to mixed effects of vitamins or other bioactive compounds such as α-carotene or lycopene, which may be more important for cancer prevention [34, 44, 45], but intake data in EPIC were not available so far. In this analysis, we conducted multiple comparisons, and some significant associations could have emerged by chance.

Strengths of the investigation are the prospective study design, the large sample size, standardised assessment methods and the verification of the endpoint data. In the EPIC calibration subsample, vitamins C and E were among the most frequent components of supplements used [41]; thus, considering overall supplement use is likely to reflect vitamin C and E supplementation.

In conclusion, we found no evidence for an overall association between intake of β-carotene, vitamin C and E and breast cancer risk in pre- and postmenopausal women in this prospective cohort study. Thus, our results are in line with the conclusions of the WCRF report of 2007 [1]. Results of subgroup analyses suggest a protective effect from high intake of vitamin C or β-carotene in some subgroups of postmenopausal women, notably those using exogenous hormones or consuming moderate to high amounts of alcohol. These results, however, have to be interpreted with caution, and further research applying biomarker measurements is needed to clarify these observations.

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