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Dietary and cancer-related behaviors of vitamin/mineral dietary supplement users in a large cohort of French women

Mathilde Touvier, Emmanuelle Kesse, Jean-Luc Volatier, Françoise Clavel-Chapelon, Marie-Christine Boutron-Ruault

■ **Summary** *Background* Several epidemiological studies suggested an association between vitamin/ mineral dietary supplement use and cancer risk. However, characteristics of supplement users may themselves be related to cancer risk, and therefore could confound such etiological studies.Very little is known about the characteristics of French supplement users. *Aim of the study* To identify cancer-related behaviors and dietary characteristics of vitamin/mineral supplement users in the E3N cohort of French women. *Methods* Data on supplement use and cancer-related and socio-demographic characteristics were collected by self-administered questionnaires completed by 83,058 women, 67,229 of whom also completed a food frequency questionnaire. Supplement users were compared to non-users by unconditional logistic regression. *Results* Vitamin/mineral supplement users were significantly older and leaner (odds ratio [OR] for BMI≥ 30 vs. <18.5 kg/m^2=0.35, 95% confidence interval [CI] 0.31–0.39), were less often current smokers, had a higher level of education and had more leisure physical activity. They used more phytooestrogen supplements (OR=3.95, 95 % CI 3.69–4.23), had more often a family history of breast cancer and had more often undergone cancer-screening.Users tended to have a healthier diet: less alcohol,more vegetables, fruit, dairy products, fish and soups. They had higher dietary intakes for most micro-nutrients, fiber and ω3 fatty acids, lower fat intake and either similar or lower prevalence of inadequate dietary intake for all relevant nutrients except magnesium. *Conclusions* To avoid major confounding, the lifestyle characteristics of supplement users should be considered in studies investigating the association between supplement use and cancer risk.

■ **Key words** dietary supplements – vitamins – minerals – neoplasms – diet

Introduction

Supplement use is increasing in France, as in many other countries throughout the world. Several epidemiological studies and randomized clinical trials have suggested that vitamin/mineral dietary supplement use might modulate the risk of several conditions including cancer and cardiovascular disease [1–4], but the results are not consistent and further research is needed.While clinical trials are essential to provide convincing evidence of the effects of supplement use on cancer risk, they have limitations, and observational studies are therefore still playing an important role in this field of investigation. In studies of this type, it is essential to control for confounding factors such as socio-demographic, cancer-related and dietary characteristics. Several studies have suggested associations between these factors and supplement use, especially in the United States [5–20].However, such investigations are less frequent in Europe [21–26], and there are hardly any data for France [27]. As inter-country differences in the profiles of supplement users could be expected, the relationship between supplement use and several dietary, socio-demographic and cancer-related factors was investigated in the E3N cohort, a large cohort of French women.

M. Touvier · J.-L.Volatier : AFSSA – French Food Safety Agency, DERNS/OCA, Maisons-Alfort, France
E.Kesse · F. Clavel-Chapelon · M.-Ch. Boutron-Ruault (✉): INSERM, Equipe E3N,EMT, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif Cedex, France, Tel.: +33-142/116-466, Fax: +33-142/114-000, E-Mail: boutron@igr.fr

Subjects and methods

■ Subjects

The E3N (Etude Epidémiologique de Femmes de la Mutuelle Générale de l'Education Nationale, MGEN) prospective cohort was initiated in France in 1990 to study the risk factors for the most frequent sites of cancer in women [28]. The cohort consists of 98,995 women living in France, aged 40 to 65 years at baseline and covered by the MGEN, the national health insurance plan for teachers and co-workers.All study subjects signed an informed consent form, in compliance with the rules of the French National Commission for Computed Data and Individual Freedom (Commission Nationale Informatique et Libertés) from which we obtained approval.

■ Data collection

The women completed self-administered mailed questionnaires approximately every 24 months since 1990.

Dietary supplement use

The 2000 questionnaire asked participants if they took supplements of any of the following nutrients at least 3 times a week: calcium,fluoride,vitamins C,D,E,B-group vitamins, beta-carotene, retinol, folic acid, other vitamins, and other minerals. They were also asked if they took phytooestrogen supplements at least 3 times a week. The questionnaire was completed by 84% of participants (n=83,058).

Cancer-related behaviors and socio-demographic characteristics

Self-administered questionnaires were used to collect data on socio-demographic characteristics (age, marital status, geographical region, level of urbanization, education, number of children), body mass index (BMI), work-related stress, frequency of cancer screening (mammography, colonoscopy, Hemoccult® test, Pap smear) and medical follow-up (bone densitometry, cholesterol and blood pressure tests) in the previous 3 years, amount of leisure physical activity (converted into minutes per day), smoking status (current/former/never), family history of breast cancer (the most frequent site of cancer in the E3N cohort) in first-degree relatives, and current use of hormone replacement therapy (HRT).

Dietary data

Dietary data were collected between June 1993 and July 1995 using a two-part self-administered questionnaire. The first part contained questions on the quantity and frequency of consumption of food groups, while the second consisted of qualitative questions, enabling the food groups to be broken down into individual food items. The questionnaire, accompanied by a booklet of photographs for the estimation of portion sizes, assessed dietary consumption of 208 food items, beverages and recipes. Both the questionnaire and the booklet were validated, and reproducibility of the questionnaire was tested after one year [29, 30].

The dietary questionnaire was sent to 95,644 women, with two reminders to non-responders. In all, 77,613 questionnaires (81.1%) were returned. After exclusion of 985 questionnaires because of absence of consent for external health follow-up by the health insurer in the case of dropout, 2050 questionnaires because of miscoded answers, 8 blank questionnaires, 46 duplicate questionnaires and 1490 questionnaires with extreme values (in the bottom 1% or top 1 %) for the ratio between energy intake and required energy (taking into account age, weight and height), 73,034 questionnaires were available for analysis. Daily dietary intakes of macro- and micro-nutrients were estimated using a food composition table derived from the French national database [31]. Responders to the dietary questionnaire are also included in the European Prospective Investigation on Cancer (EPIC) [32].

■ Analysis

Cancer-related behaviors and socio-demographic characteristics of supplement users

Supplement users and non-users among the 83,058 women who answered the dietary supplement questionnaire were compared on socio-demographic and behavioral characteristics. Missing values for variables with less than 5% of missing values were replaced by the modal value. For other variables with missing values (marital status, 6.4%; work-related stress, 7.1 %), a separate class was created for missing values and entered in the models. However, we checked that results were unchanged when subjects with one or more missing values for any variable were excluded from the analyses.

Dietary characteristics of supplement users

Analyses of dietary characteristics were based on the 67,229 women for whom supplemental and dietary data was available. Mean intakes of 17 food groups, micro and macro-nutrients, energy, dietary fiber and alcohol were calculated for users and non-users of dietary supplements. The proportion of subjects whose daily dietary intake was below the estimated average requirement (EAR) was calculated for each nutrient for users and non-users of supplements. Although this EAR cutpoint does not allow to classify an individual as having adequate or inadequate intake, it has been demonstrated that the proportion of subjects below EAR corresponds to an unbiased estimation of the prevalence of inadequate dietary nutrient intake in the studied population [33, 34]. The U.S. Food and Nutrition Board (FNB) values for EAR were used when available [35], i. e. except in the case of calcium and pantothenic acid. For these two nutrients, the French EAR values were used [36]. Prevalence of inadequate intake could not be defined for vitamin D because of endogenous synthesis. Mean intakes of dietary beta-carotene, retinol, vitamins C, D and E, folate and calcium, and prevalence of inadequate intake for vitamins A, C, E, folate and calcium were also calculated, for users and non-users of the particular nutrient in supplemental form.

Supplement users and non-users were compared in cross-sectional analyses, using unconditional logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs). All results were considered significant at the 5% level.The SAS version 8.2 software package was used for all statistical analyses.

Results

■ Cancer-related behaviors and socio-demographic characteristics of supplement users

The study population (n=83,058) is described in Table 1 by supplement use. The average age was 60.7±6.8 years for supplement users and 59.2±6.5 years for non-users. The proportion of subjects who took supplementation was 12.5 % for calcium, 0.6% for fluoride, 6.3 % for vitamin C, 5.5% for vitamin E, 4.4% for vitamin D, 3.7% for B-group vitamins except folic acid, 3.1% for retinol, 2.5% for beta-carotene, 1% for folic acid, 11.8 % for other minerals and 1.9 % for other vitamins. Overall, supplement users represented 26.9% of the study population, 90.8% of the women were postmenopausal, and 42.5% were retired, a characteristic associated with higher supplement use ($p<0.05$).However, the association was not significant after adjustment for age.

As compared to non-users, users were more likely to be older, to live alone, to have no or few children, to live in the Mediterranean region and to live in cities of more than 10.000 inhabitants. Supplement users were less likely to live in Central, North-West or South-West France. They more often perceived their work as stressful. They tended to have a higher level of education and a lower BMI. They were more often former or never smokers and more often engaged in leisure physical activity. Women who took supplements were more likely to have had a family history of breast cancer. They were also more likely to have had a mammography, a colonoscopy, a Pap smear, a bone densitometry test, a Hemoccult® test, or a cholesterol or blood pressure test in the previous 3 years. They took less HRT and more phytooestrogen supplements than non-users of vitamin/mineral supplements.

As there was a strong colinearity among variables related to frequency of cancer-screening/medical follow-up, only 'mammography' (chosen because of specific interest in breast cancer in our cohort) was entered in the multivariate model. All variables remained significant in the multivariate model (Table 1).

Calcium and vitamin D supplements are probably often medically prescribed for specific prevention or treatment of osteoporosis in this population of women aged about 60. Thus, calcium or vitamin D users may not have all the characteristics of typical supplement users. The analyses were therefore also performed excluding users of calcium and/or vitamin D only. Analysis of the remaining 76,205 women (20.3% of supplement users) gave similar results (data not tabulated), except for family history of breast cancer and current use of HRT, both of which were no longer statistically significant, with ORs of 1.01 (95 % CI 0.96–1.07) and 0.98 (95% CI 0.95–1.02) respectively.

■ Dietary characteristics of supplement users

Supplement users were more likely to follow a restrictive diet to lose weight (age-adjusted OR=1.10, 95% CI 1.02–1.18, p=0.0091), or to be vegetarians (age-adjusted OR=2.52, 95% CI 2.01–3.16, $p<0.0001$), as compared to non-users.

Table 1 **Comparison of supplement users (n = 22,302) and non-users (n = 60,756) on socio-demographic and cancer-related variables**

	Non-users (%)	Users (%)	Age-adjusted logistic regression analyses			Multivariate logistic regression analysis[g]		
			OR (95% CI)	p	p for trend[h]	OR (95% CI)	p	p for trend[h]
Age[a]				< 0.0001	< 0.0001		< 0.0001	< 0.0001
< 55.2 years	35.4	27.6	1.00			1.00		
55.2–62.2 years	33.9	32.2	1.22 (1.17–1.27)			1.28 (1.23–1.34)		
> 62.2 years	30.7	40.1	1.68 (1.61–1.74)			1.89 (1.82–1.97)		
Marital status[b]				< 0.0001			< 0.0001	
Married or with partner	78.1	73.8	1.00			1.00		
Single	21.9	26.2	1.22 (1.18–1.27)			1.18 (1.14–1.23)		
Geographical region				< 0.0001			< 0.0001	
Paris area	18.1	19.0	1.00			1.00		
Overseas depts/territories/Corsica	0.3	0.4	1.22 (0.95–1.57)			1.23 (0.95–1.60)		
Center	11.5	10.2	0.84 (0.80–0.90)			0.88 (0.83–0.94)		
Mediterranean	13.2	16.4	1.16 (1.10–1.22)			1.12 (1.06–1.19)		
North	7.0	6.5	0.89 (0.83–0.96			0.99 (0.92–1.06)		
North-East	11.7	11.3	0.94 (0.89–1.00)			1.02 (0.96–1.09)		
North-West	13.9	11.4	0.78 (0.74–0.82)			0.83 (0.78–0.88)		
South-East	10.4	11.6	1.06 (1.00–1.13)			1.05 (0.99–1.12)		
South-West	13.9	13.3	0.90 (0.85–0.95)			0.90 (0.85–0.95)		
Level of urbanization				< 0.0001			0.0089	
≤ 10,000 inhabitants	60.5	57.4	1.00			1.00		
> 10,000 inhabitants	39.5	42.6	1.11 (1.08–1.15)			1.05 (1.01–1.09)		
Number of years of education				< 0.0001	< 0.0001		< 0.0001	< 0.0001
None	0.7	0.4	1.00			1.00		
5 years	4.0	3.2	1.25 (0.99–1.58)			1.20 (0.94–1.52)		
9 years	8.3	7.9	1.57 (1.25–1.98)			1.41 (1.12–1.78)		
12–14 years	52.8	52.8	1.69 (1.35–2.11			1.37 (1.09–1.72)		
15–16 years	17.7 16.5	17.3	1.79 (1.43–2.24)			1.41 (1.12–1.78)		
≥ 17 years		18.4	1.92 (1.54–2.40)			1.50 (1.19–1.89)		
Number of children				< 0.0001	< 0.0001		< 0.0001	< 0.0001
0	19.5	22.4	1.00			1.00		
1	14.3	15.9	0.99 (0.94–1.05)			1.00 (0.95–1.06)		
2	39.3	37.6	0.87 (0.84–0.91)			0.91 (0.87–0.95)		
3	19.7	17.8	0.79 (0.75–0.83)			0.84 (0.80–0.89)		
4	5.3	4.6	0.71 (0.66–0.77)			0.80 (0.74–0.87)		
≥ 5	2.0	1.7	0.64 (0.57–0.72)			0.75 (0.66–0.85)		
Body Mass Index (kg/m^2)				< 0.0001	< 0.0001		< 0.0001	< 0.0001
< 18.5	2.5	4.2	1.00			1.00		
18.5-24.9	64.9	70.9	0.65 (0.60–0.71)			0.65 (0.60–0.71)		
25-29.9	25.1	20.6	0.47 (0.43–0.51)			0.48 (0.44–0.53)		
≥30	7.5	4.3	0.33 (0.30–0.37)			0.35 (0.31–0.39)		
Perception of work-related stress[c]				< 0.0001			< 0.0001	
Not or not very stressful	18.3	15.9	1.00			1.00		
Stressful	59.0	57.7	1.12 (1.07–1.17)			1.11 (1.06–1.16)		
Very stressful	22.7	26.4	1.33 (1.26–1.39)			1.31 (1.24–1.38)		
Smoking status				< 0.0001			< 0.0001	
Current smoker	9.8	8.5	1.00			1.00		
Former smoker	25.6	26.3	1.14 (1.07–1.21)			1.17 (1.10–1.25)		
Never smoker	64.6	65.3	1.08 (1.02–1.14)			1.14 (1.08–1.21)		
Leisure physical activity				< 0.0001	< 0.0001		< 0.0001	< 0.0001
0 min/day	52.0	49.8	1.00			1.00		
< 43 min/day[d]	21.7	22.8	1.14 (1.09–1.18)			1.07 (1.02–1.11)		
≥43 min/day	26.2	27.4	1.14 (1.10–1.18)			1.09 (1.05–1.13)		
Current use of hormone replacement therapy				< 0.0001			< 0.0001	
No	47.1	51.2	1.00			1.00		
Yes	52.9	48.8	0.91 (0.88–0.94)			0.91 (0.88–0.94)		
Current use of phytooestrogens				< 0.0001			< 0.0001	
No	97.3	90.4	1.00			1.00		
Yes	2.7	9.6	4.24 (3.96–4.53)			3.95 (3.69–4.23)		
Family history of breast cancer[e]				0.001			0.0368	
No	88.0	87.0	1.00			1.00		
Yes	12.0	13.0	1.08 (1.03–1.13)			1.05 (1.00–1.10)		
Mammography[f]				< 0.0001			< 0.0001	
No	14.1	12.5	1.00			1.00		
Yes	85.9	87.5	1.26 (1.20–1.32)			1.24 (1.18–1.30)		
Pap smearf				< 0.0001				
No	24.1	22.5	1.00					
Yes	75.9	77.5	1.24 (1.19–1.29)					
Bone densitometry test[f]				< 0.0001				
No	82.6	61.2	1.00					
Yes	17.4	38.8	2.87 (2.77–2.97)					

Table 1 *Continued*

	Non-users (%)	Users (%)	Age-adjusted logistic regression analyses: OR (95% CI)	p	p for trend[h]	Multivariate logistic regression analysis[g]: OR (95% CI)	p	p for trend[h]
Cholesterol test[f]				< 0.0001				
No	40.8	35.4	1.00					
Yes	59.2	64.6	1.22 (1.19–1.26)					
Blood pressure test[f]				< 0.0001				
No	13.6	10.6	1.00					
Yes	86.5	89.4	1.32 (1.25–1.38)					
Hemoccult® test[f]				< 0.0001				
No	88.1	86.2	1.00					
Yes	11.9	13.8	1.17 (1.11–1.22)					

[a] Cut-off points correspond to tertiles determined on the whole study population
[b] Because of missing values, the proportions of subjects for 'marital status' were calculated on 20,921 supplement users and 56,836 non-users
[c] Because of missing values, the proportions of subjects for 'perception of work-related stress' were calculated on 20,776 supplement users and 56,351 non-users
[d] 43 min/day = median for sportswomen
[e] In first degree relatives (parents, children, brothers and sisters)
[f] In the previous 3 years
[g] The multivariate model was a full model including all variables from the age-adjusted analysis, except colonoscopy, Hemoccult® test, Pap smear, bone densitometry, cholesterol and blood pressure tests. Indeed, as there was a strong colinearity among variables related to frequency of cancer-screening/medical follow-up, only 'mammography' (chosen because of specific interest in breast cancer in our cohort) was entered as cancer-screening/medical follow-up variable in the multivariate model
[h] Tests for linear trend were performed using the ordinal score on categories of each variable

Table 2 presents the comparison of supplement users and non-users on the consumption of 17 food groups,by logistic regression analysis adjusted for age and energy intake. Users of dietary supplements ate less meat and potatoes and drank less alcohol than non-users. They also ate more vegetables, fruit, dairy products, fish, soup, sugar and confectionary and drank more soft drinks (except sodas). Results without adjustment for energy were similar (not tabulated).

Table 2 **Comparison of supplement users (n = 17,998) and non-users (n = 49,231) by tertiles of daily food intake, using logistic regression analysis adjusted for age and energy intake[a]**

	Non-users: Mean (g/day)	Non-users: ± SD	Users: Mean (g/day)	Users: ± SD	OR T2[b] (95% CI T2)	OR T3[b] (95% CI T3)	p for trend
Potatoes	64.2	48.8	61.3	49.3	0.91 (0.87–0.95)	0.85 (0.81–0.89)	< 0.0001
Vegetables	281.4	133.7	290.6	138.8	1.07 (1.03–1.12)	1.13 (1.08–1.18)	< 0.0001
Dried vegetables	18.7	21.5	19.3	22.8	1.00 (0.96–1.04)	1.08 (1.04–1.13)	0.0004
Fruits	262.5	163.8	279.7	174.9	1.06 (1.02–1.11)	1.16 (1.11–1.21)	< 0.0001
Dairy products	315.0	198.0	321.6	207.7	0.99 (0.95–1.03)	1.07 (1.02–1.11)	0.0037
Cereals	209.5	102.3	206.8	103.3	0.99 (0.95–1.04)	0.98 (0.94–1.03)	0.5056
Meat	108.4	57.7	101.1	56.8	0.89 (0.85–0.92)	0.76 (0.72–0.79)	< 0.0001
Fish	36.9	26.5	38.8	28.1	1.05 (1.01–1.10)	1.16 (1.12–1.22)	< 0.0001
Eggs	26.0	21.4	25.6	21.6	0.99 (0.95–1.03)	0.98 (0.94–1.02)	0.3819
Fats	16.4	10.2	16.3	10.0	1.01 (0.96–1.05)	1.02 (0.98–1.07)	0.4115
Sugar and confectionary	39.4	31.9	40.1	32.1	1.08 (1.04–1.13)	1.11 (1.06–1.16)	< 0.0001
Cakes/biscuits	38.1	35.2	38.0	35.7	1.03 (0.99–1.08)	1.03 (0.98–1.07)	0.2474
Sodas[c]	9.5	45.2	8.9	42.7	1.06 (1.00–1.13)	0.99 (0.93–1.05)	0.7768
Soft drinks (except sodas)	1387.3	645.9	1440.3	681.7	1.06 (1.01–1.10)	1.22 (1.17–1.27)	< 0.0001
Alcoholic drinks	130.4	169.8	122.5	164.1	0.98 (0.94–1.03)	0.90 (0.86–0.94)	< 0.0001
Condiments and sauces	25.0	13.1	24.9	13.2	1.01 (0.96–1.05)	1.05 (1.00–1.09)	0.0522
Soups	109.4	111.2	119.1	115.9	1.05 (1.01–1.10)	1.14 (1.09–1.19)	< 0.0001

[a] The probability of being a supplement user is modeled
[b] T2 = tertile 2 of the food group, T3 = tertile 3. Reference = tertile 1
[c] Because of the high percentage of non-consumers, it was not possible to obtain balanced tertiles for this variable. The population was therefore split into 3 groups: Nonconsumers (81.3%)/Consumption <19.70g/day (8.7%)/Consumption ≥19.70g/day (10%). 19.7g/day being the median of consumption among soda consumers

Table 3 presents the results of the comparison of supplement users and non-users on dietary nutrient intake, by logistic regression analysis adjusted for age and energy intake. Overall, supplement users had higher dietary intakes of beta-carotene, thiamin, pantothenic acid, vitamins B6, C and D, folate, calcium, iron, phosphorus, ω3 fatty acids, total and simple carbohydrates and dietary fiber than non-users. On the other hand, they had lower intakes of retinol, niacin, vitamin B12, magnesium, alcohol, starch, proteins, total lipids, saturated, poly-unsaturated and ω6 fatty acids.Results without adjustment for energy intake were similar, except for proteins, which became statistically non-significant (data not tabulated). Users of beta-carotene, vitamin C, vitamin D or folic acid supplements had a higher dietary intake for the nutrient in question.

Table 3 **Comparison of supplement users and non-users by tertiles of daily energy and dietary nutrient intake (n = 67,229), using logistic regression analysis adjusted for age and energy intake[a]**

	Non-users		Users		OR T2[b] (95% CI T2)	OR T3[b] (95% CI T3)	p for trend
	Mean	± SD	Mean	± SD			
Overall use of supplements					OR for supplement use		
Energy (kcal)	2113.5	553.1	2094.6	552.3	0.99 (0.95–1.03)	0.99 (0.95–1.03)	0.5736
Alcohol (g)	11.3	14.2	10.6	13.6	0.98 (0.94–1.02)	0.89 (0.85–0.93)	< 0.0001
Total carbohydrates (g)	230.6	73.2	232.0	73.8	1.08 (1.03–1.13)	1.20 (1.13–1.28)	< 0.0001
Simple carbohydrates (g)	100.2	35.0	103.3	36.3	1.13 (1.08–1.18)	1.34 (1.27–1.40)	< 0.0001
Starch (g)	124.4	51.9	122.4	51.9	0.95 (0.91–1.00)	0.94 (0.89–0.99)	0.0169
Fibers (g)	24.0	7.7	24.8	8.1	1.16 (1.11–1.21)	1.37 (1.31–1.45)	< 0.0001
Proteins (g)	91.5	25.5	90.4	25.5	0.98 (0.93–1.02)	0.93 (0.88–0.99)	0.0232
Total lipids (g)	89.3	27.5	87.7	27.4	0.93 (0.89–0.98)	0.88 (0.83–0.94)	0.0001
Saturated fatty acids (g)	35.8	12.9	34.8	12.8	0.90 (0.86–0.95)	0.85 (0.81–0.91)	< 0.0001
Mono unsaturated fatty acids (g)	32.0	10.6	31.8	10.7	0.97 (0.93–1.02)	1.03 (0.98–1.10)	0.2834
Poly unsaturated fatty acids (g)	16.0	6.4	15.5	6.3	0.91 (0.87–0.95)	0.84 (0.80–0.88)	< 0.0001
ω6 fatty acids (g)	14.2	6.1	13.7	5.9	0.90 (0.86–0.94)	0.84 (0.80–0.88)	< 0.0001
ω3 fatty acids (g)	1.5	0.6	1.5	0.6	1.03 (0.99–1.08)	1.09 (1.04–1.15)	0.0006
Beta-carotene (µg)	3926.4	1733.6	4105.4	1799.4	1.10 (1.05–1.14)	1.21 (1.16–1.27)	< 0.0001
Retinol (µg)	1166.4	1123.8	1140.0	1150.5	0.87 (0.84–0.91)	0.89 (0.85–0.93)	< 0.0001
Thiamin (mg)	1.3	0.4	1.3	0.4	1.06 (1.01–1.11)	1.26 (1.19–1.33)	< 0.0001
Riboflavin (mg)	2.2	0.7	2.2	0.7	0.98 (0.94–1.03)	1.04 (0.99–1.10)	0.0808
Niacin (mg)	24.9	9.8	24.0	9.7	0.87 (0.83–0.91)	0.82 (0.78–0.86)	< 0.0001
Pantothenic acid (mg)	5.6	1.6	5.6	1.6	1.06 (1.01–1.11)	1.21 (1.15–1.28)	< 0.0001
Vitamin B6 (mg)	1.8	0.5	1.8	0.5	1.09 (1.04–1.14)	1.30 (1.23–1.37)	< 0.0001
Folate (µg)	406.0	117.7	414.7	121.6	1.11 (1.06–1.16)	1.27 (1.21–1.33)	< 0.0001
Vitamin B12 (µg)	8.1	5.1	8.0	5.2	0.92 (0.88–0.96)	0.93 (0.89–0.97)	0.0012
Vitamin C (mg)	138.3	60.3	146.4	65.2	1.10 (1.06–1.15)	1.28 (1.23–1.34)	< 0.0001
Vitamin D (µg)	2.6	1.3	2.6	1.3	1.02 (0.98–1.07)	1.11 (1.06–1.16)	< 0.0001
Vitamin E (mg)	14.2	5.9	14.1	5.8	1.03 (0.99–1.08	) 0.99 (0.94–1.03)	0.5577
Calcium (mg)	1011.4	355.8	1025.6	367.6	1.06 (1.02–1.11)	1.14 (1.09–1.20)	< 0.0001
Iron (mg)	13.9	3.8	14.0	3.9	1.07 (1.02–1.13)	1.26 (1.18–1.34)	< 0.0001
Magnesium (mg)	424.6	142.3	418.1	142.6	0.93 (0.89–0.98)	0.91 (0.87–0.96)	0.0002
Phosphorus (mg)	1391.7	385.6	1394.0	392.1	1.07 (1.02–1.12)	1.19 (1.12–1.26)	< 0.0001
Supplemental use of the specific nutrient					OR for supplemental use of the specific nutrient		
Beta-carotene (µg)	3968.5	1748.5	4201.2	1918.3	1.04 (0.92–1.18)	1.32 (1.17–1.49)	< 0.0001
Retinol (µg)	1158.7	1126.0	1178.9	1281.8	0.90 (0.80–1.00)	0.90 (0.81–1.01)	0.0825
Folate (µg)	408.1	118.7	429.8	133.8	1.21 (0.98–1.48)	1.67 (1.34–2.07)	< 0.0001
Vitamin C (mg)	139.8	61.2	151.2	68.9	1.14 (1.05–1.24)	1.50 (1.38–1.62)	< 0.0001
Vitamin D (µg)	2.6	1.3	2.7	1.4	1.11 (1.01–1.22)	1.17 (1.06–1.29)	0.0014
Vitamin E (mg)	14.2	5.9	14.1	5.9	1.02 (0.93–1.10)	0.97 (0.89–1.06)	0.5433
Calcium (mg)	1017.3	359.7	1000.1	354.1	1.04 (0.98–1.10)	0.98 (0.92–1.04)	0.5162

[a] The probability of being a supplement user is modeled; [b] T2 = tertile 2 of the food group, T3 = tertile 3. Reference = tertile 1

Table 4 presents the comparison of the prevalence of inadequacy of dietary nutrient intake between supplement users and non-users, by logistic regression analysis adjusted for age and energy. Overall,after adjustment for age and energy, prevalence of inadequacy was statistically significantly lower in supplement users compared with non-users for calcium, vitamins C and B6, folate and thiamin, and higher for magnesium, riboflavin, niacin and vitamin B12. However, for the latter three nutrients, the prevalence of inadequacy was very low (less than 5 %) for both users and non-users. Users of folic acid or calcium supplements had a significantly lower prevalence of inadequate dietary intake for the nutrient in question. Results without adjustment for energy intake were similar, except in the case of thiamin for supplement users in general, and of calcium for users of calcium supplements (these results were non-significant in models without adjustment for energy, data not tabulated).

Stability of supplement use as assessed by a similar question two years later was quite good: 73.3% of the users were still consumers, while only 21.8% of nonusers became consumers.

Table 4 **Comparison of the prevalence of dietary nutrient inadequacy between supplement users and non-users (n = 67,229) by logistic regression analysis adjusted for age and energy intake[a]**

	Prevalence of inadequacy[b] (%)		OR (95% CI)	p
	Non-users	Users		
Overall use of supplements			OR for inadequacy[c]	
Total vitamin A	1.05	1.14	1.07 (0.91–1.26)	0.4108
Thiamin	12.55	12.59	0.94 (0.88–0.99)	0.0260
Riboflavin	0.44	0.64	1.36 (1.08–1.70)	0.0091
Niacin	3.64	4.54	1.21 (1.10–1.32)	< 0.0001
Pantothenic acid	12.12	12.15	0.95 (0.90–1.01)	0.1220
Vitamin B6	13.94	13.40	0.90 (0.85–0.96)	0.0004
Folate	23.55	21.74	0.87 (0.83–0.91)	< 0.0001
Vitamin B12	1.28	1.81	1.38 (1.20–1.58)	< 0.0001
Vitamin C	5.31	4.59	0.87 (0.80–0.95)	0.0010
Vitamin E	40.49	40.84	1.00 (0.96–1.03)	0.8317
Calcium[e]	35.60	36.48	0.89 (0.86–0.93)	< 0.0001
Iron	0.08	0.14	1.59 (0.96–2.62)	0.0702
Magnesium	9.69	10.66	1.08 (1.02–1.15)	0.0129
Phosphorus	0.38	0.46	1.13 (0.87–1.47)	0.3497
Supplemental use of the specific nutrient			OR for inadequacy[d]	
Total vitamin A	1.07	1.14	1.04 (0.74–1.47)	0.8194
Folate	23.10	19.10	0.70 (0.56–0.86)	0.0009
Vitamin C	5.12	5.04	0.98 (0.85–1.13)	0.7762
Vitamin E	40.53	41.37	1.00 (0.93–1.08)	0.9381
Calcium[e]	35.00	41.70	0.95 (0.90–1.00)	0.0439

[a] The probability of dietary nutrient intake below the estimated average requirement (EAR) is modeled (corresponding to the prevalence of dietary nutrient inadequacy at the population level)
[b] U. S. Food and Nutrition Board EARs were used when available and French EARs were used in other cases (i. e., for calcium and pantothenic acid)
[c] Reference = non-supplement user
[d] Reference = non-supplement user of the nutrient in question
[e] Crude prevalences of inadequate intake given in columns 2 and 3 are not adjusted for age nor for energy, whereas ORs from the logistic regression analysis (column 4) are adjusted for these two variables. This explains the apparent inconsistency for calcium between ORs and crude prevalences of inadequacy

Discussion

About 27% of subjects in the E3N sample were vitamin or mineral supplement users, as defined here as in similar cross-sectional studies, i.e at least 3 times a week [6,7]; the proportion remained as high as 20% when women who took only calcium and/or vitamin D supplements were excluded.Very few data are available on the prevalence of dietary supplement use in the general French population.A 2002 study based on a representative sample of French adults of all ages and both sexes reported that approximately 10% of the subjects had taken at least one vitamin-mineral supplement in the 2 weeks before the interview [37]. Two factors may account for the higher proportion of supplement users in the E3N cohort. First, the subjects in the E3N study are women, are older and are well educated, three characteristics that are strong predictors of supplement use [11, 12].Secondly, supplement users are more likely to be interested in health matters and are therefore more likely to participate in a large cohort study on cancer risk. As expected, even in the E3N sample, supplement use was lower than in some other countries, especially the United States, where over 40% of people use supplements [11, 38] and 34% took daily vitamin or mineral supplements in 2000 [16]. Calcium was the most frequently used nutrient, which is consistent with the fact that our population of women aged about 60 was likely to require calcium supplementation for the prevention or treatment of osteoporosis.

Several socio-demographic characteristics and cancer-related behaviors were significantly related to dietary supplement use in our study. Users of dietary supplements tended to have a healthier lifestyle than non-users, as already described in other countries. In agreement with our findings, many studies have reported that supplement users tended to have a lower BMI, to be engaged in more leisure physical activity and were more likely to be former or non-smokers rather than current smokers [8, 20–22, 25, 27, 39–41]. Several studies in other countries also found that supplement users were older, had a higher level of education and were more likely to consider their job as stressful [6, 9, 11, 12, 27, 39, 41].Previous studies in other countries also reported that women who took supplements were more likely to have had a family history of breast cancer and to have a higher frequency of medical follow-up/cancerscreening [5, 6, 8, 39].

Several studies in the United States noted a positive association between HRT and dietary supplement use [5, 8].We observed the opposite in our study, mostly because HRT use was inversely related to calcium and/or vitamin D intake. Indeed, the inverse relationship observed between supplement use and HRT ceased to be statistically significant when users of calcium and/or vitamin D only were excluded. This is consistent with previous findings that HRT use protects against osteoporosis [42], thus reducing the need for calcium supplementation. Except for this point and for family history of breast cancer (which became non-significant due to a loss of power), the profile of supplement users was similar when including or excluding calcium/vitamin D only users.

Users of dietary supplements tended to have a healthier diet than non-users: they drank less alcohol and ate more vegetables, fruit, dairy products, fish and soup. Even without considering supplements, they had higher dietary intakes for many vitamins and minerals, fiber, and ω3 fatty acids and a lower fat intake. They were also more likely to be involved in specific diets such as vegetarianism (1.1 % in supplement users vs. 0.5% in nonusers). Higher sugar intake was the only aspect not consistent with a healthier dietary pattern, but in agreement with a previously published study [22]. As far as nutrients with a relevant prevalence of inadequate intake (> 5%) were concerned, dietary inadequacy was higher among supplement users only for magnesium and was either similar or lower (for calcium,vitamin C, B6, folate and thiamin) for other nutrients, after adjustment for age and energy.Most studies in other countries have reported that supplement users had a healthier diet than non-users,and thus that they might be less likely to need nutrient supplementation [6, 11, 13, 14, 22, 23, 26, 43]. Dietary supplement use was also associated with vegetarianism in previous studies [15, 22]. The dietary restrictions implicit in vegetarian diets might explain the greater likelihood of use of dietary supplements in a particularly health conscious group, because of concerns about nutrient adequacy.

It has been demonstrated that the EAR was the most appropriate cut-off point for obtaining a non-biased estimate of the prevalence of nutrient inadequacy [33]. This method is most accurate if the requirement distribution is symmetrical, the variability in intake is greater than the variability in requirement, and intake and requirement are independent [33]. These conditions were globally satisfied for all the studied nutrients, although less accurately so for iron, particularly because of limitations of the symmetry condition. Our estimation of dietary inadequacy for iron should therefore be considered with caution. Accuracy of the measurement of the prevalence of inadequacy also depends on the quality of dietary data. We used a detailed and validated qualitative and quantitative questionnaire, with special care in the estimation of portion size. Besides, we were more concerned with comparing users and non-users than with providing a precise estimate of prevalence of inadequacy.

Several studies have noted that both fortified foods and vitamin/mineral dietary supplements could improve the nutritional status in case of insufficient dietary micronutrient intake, but could also be responsible for excessive and potentially toxic levels of intake for some micronutrients [23, 44–47]. The characteristics of supplement users are therefore of great interest with a view to surveillance, especially their already higher intakes of most micro-nutrients from food. It was interesting to note that the characteristics of supplement users were similar to those observed in other countries (including on representative samples), as inter-country differences in the profiles of supplement users could have been expected. Although our study primarily involved teachers, who have a higher level of education and a healthier lifestyle than the general female population of the same age, it provided important information for surveillance purposes, given the paucity of data available on this subject for France.

Our results suggest that the profiles of supplement users are quite similar across different countries, regardless of the level of supplement use in the general population. They demonstrate the need to carefully control for many variables when investigating the association between dietary supplement use and chronic conditions such as cancer, one of the objectives of the E3N cohort. There are many ways in which the observed associations could confound studies of supplement use and cancer risk. Cancer screening can lead to over-estimation of incidence by detecting early lesions, but also to reduced mortality by affecting the stage at which the disease is diagnosed. For example, as supplement users were more likely to have had a mammography, further studies on supplement use and breast cancer incidence or mortality should carefully adjust for frequency of mammography. A 'healthy supplement user effect' (higher physical activity, lower tobacco use, healthy dietary pattern, etc.) might also be defined, which could lead to the erroneous conclusion of an inverse association between supplement use and cancer or cardiovascular disease. On the other hand, supplements may exert real protective or deleterious effects on cancer risk, and therefore act as confounding factors in analyses of the link between cancer and different exposures, such as physical activity, tobacco use, or dietary intake.To avoid major confounding, it is therefore essential that studies investigating the association between chronic disease and environmental factors including diet and supplements take into account the dietary and lifestyle characteristics of supplement users.

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