

## Dietary supplement use among cancer survivors of the NutriNet-Santé cohort study

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### Abstract

Dietary supplements (DS) may influence cancer prognosis. Their use in cancer patients has been described in the United States, but data are largely lacking in Europe and notably in France. The present study's objectives were (1) to assess DS use and its sociodemographic, lifestyle, and dietary correlates in a large sample of French cancer survivors; (2) to evaluate the involvement of physicians in such DS use; and (3) to assess the extent of potentially harmful practices. Data were collected by self-administered web-based questionnaires among participants of the NutriNet-Santé cohort. Data on DS use was available for 1081 cancer survivors. DS users were compared to non-users with unconditional logistic regressions. DS use was reported by 62% of women and 29% of men. Vitamins D, B<sub>6</sub>, C and Mg were the most frequently consumed nutrients. 14% of cancer survivors initiated DS use after diagnosis. For 35% of the DS consumed, subjects did not inform their attending physician. DS use was associated with a healthier lifestyle (normal weight, never smoking and better diet) and substantially contributed to nutrient intake. 18% of DS users had potentially harmful DS use practices, such as the simultaneous use of vitamin E and anticoagulant/antiplatelet agents, the use of  $\beta$ -carotene and smoking or the use of phyto-oestrogens in hormone-dependent cancer patients. The present study suggests that DS use is widespread among cancer survivors, a large amount of that use is performed without any medical supervision and a substantial proportion of that use involves potentially harmful practices. Physicians should be encouraged to more routinely discuss DS use with their cancer patients.

**Key words:** Dietary supplements: Motivations: Correlates: Cancer survivors

When disconcerted by their illness and disappointed by traditional medicine, cancer patients can move towards complementary and alternative medicines, including the use of dietary supplements (DS). However, the impact of DS on cancer prognosis, risk of recurrence and risk of second cancer remains unclear<sup>(1)</sup>. Although the beneficial effects of DS taken during or after cancer treatment are not excluded<sup>(2–4)</sup>, several studies have reported adverse effects of some DS on cancer prognoses<sup>(1,5–8)</sup>. Presently, it is recommended that phyto-oestrogen DS should be avoided with hormone-dependent cancer patients<sup>(6,9)</sup>. Similarly,  $\beta$ -carotene DS should not be used with cancer patients or with healthy people who are smokers<sup>(10–12)</sup>. In addition, studies have shown that some vitamin/mineral or herbal DS may interact

with anti-cancer or other active treatments<sup>(9,13–15)</sup>. This may be particularly problematic if attending physicians have no knowledge of the self-medication practices in their patients. According to a recent review of US studies, 56–68% of physicians are not aware of DS use among their cancer patients<sup>(16)</sup>.

In this context, it is essential to assess DS use and its correlates in cancer patients and survivors. Such observational studies have been published in the United States<sup>(8,16–21)</sup>. A recent review showed that DS use was widespread in American cancer patients, with a prevalence of vitamin and mineral DS use that varied between 64 and 81%<sup>(16)</sup>. Between 14 and 32% of the survivors began taking their supplements after diagnosis<sup>(16)</sup>. Fewer studies provided information on DS use in cancer patients in European countries<sup>(22–28)</sup>, but those

**Abbreviation:** DS, dietary supplements.

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that did showed a prevalence of DS use that varied from 9 to 48% across countries.

Several sociodemographic and lifestyle characteristics, such as female sex, higher education level and higher income, have been reported to be associated with the use of DS. However, no epidemiological study has been published for France on this topic. Perceptions and attitudes towards food and nutrition may vary significantly across countries. Thus, specific research is needed, especially in the context of the increasing availability of DS from traditional distribution channels but also from Internet sources.

The objectives of the present study were (1) to assess DS use and its sociodemographic, lifestyle and dietary correlates in a large sample of French cancer survivors involved in the NutriNet-Santé cohort; (2) to evaluate the role and involvement of physicians in DS use by their cancer patients; (3) to assess the extent of potentially harmful practices, such as use of  $\beta$ -carotene DS in smokers, the use of phyto-oestrogen DS in hormone-dependent cancer patients and contraindicated DS–medication simultaneous use.

## Methods

### Subjects

The NutriNet-Santé study is a population-based prospective observational cohort that is followed via the Internet (<http://www.etude-nutrinet-sante.fr>). Its main objective is to assess the relationships between nutrition and chronic disease risk as well as the determinants of eating behaviour<sup>(29)</sup>. It was launched in France in May 2009. Using mass-media campaigns, adults aged 18 years or older who had access to the Internet were invited to participate. All subjects signed an electronic informed consent. The NutriNet-Santé study was approved by the Institutional Review Board of the French Institute for Health and Medical Research (no. 0000388FWA00005831) and the Commission Nationale de l'Informatique et des Libertés (no. 908450 and no. 909216).

### Data collection

Participants completed several self-administered web-based questionnaires at baseline and then regularly during the follow-up. All baseline questionnaires were tested and compared against traditional assessment methods (paper questionnaires or interviews by a dietitian)<sup>(30–32)</sup>.

**Case ascertainment.** Participants self-declared any cancer diagnoses during the study follow-up through regular questionnaires and a permanent web-interface. Medical data were then gathered from participants, physicians, and/or hospitals and reviewed by an independent physician expert committee. Pathological reports were used to validate cancer cases and to extract cancer clinical data. Cases were classified using the International Chronic Diseases Classification, 10th Revision, Clinical Modification (ICD-10)<sup>(33)</sup>.

**Dietary supplement and medication use.** The questionnaire that assessed DS and medication use, which was specifically designed for cancer survivors, was sent in January

2014 to all first-incident primary cancer cases (who were diagnosed after their enrolment in the cohort). In the present study, we considered as DS both regular DS and medicinal supplements that are mainly composed of vitamins and minerals, which are treated as pharmaceutical products in France. In contrast, clinical oral nutritional supplements, such as Renutryl<sup>®</sup> or Clinutren<sup>®</sup>, were not considered as DS in the survey. Indeed, these specific products, which are rich in energy and/or protein, are administered to undernourished patients to stimulate weight gain and avoid malnutrition.

Participants were asked about their DS use at the time that they completed of the questionnaire ('current use'). In addition, cancer patients were asked to report their DS use since the date of their cancer diagnosis. For each DS, they reported the commercial name, brand, form, number of days of use per year, and number of units per day of use. The questionnaire included an assessment of the circumstances and motivations for DS use (close-ended questions) as well as questions about DS use changes after cancer diagnosis. For each DS, participants were asked if they had told at least one of their attending physicians about their DS use and, when appropriate, the reasons why they did not. Subjects also reported all anti-cancer or other medications (chosen among an exhaustive list based on the VIDAL, a French drug reference database<sup>(34)</sup>) that they were taking at the time of the DS questionnaire. A DS composition database was created and implemented based on information found on official brands' websites or direct contact with manufacturers.

**Sociodemographic, lifestyle and anthropometric data.** Self-administered questionnaires were annually administered during follow-up to collect and update data on sociodemographic, lifestyle and behavioural characteristics, including sex, age, geographical region, marital status, number of children, educational level, smoking status, anthropometry and leisure-time physical activity (which was estimated with the validated international physical activity questionnaire<sup>(35)</sup>). Data collected after cancer diagnosis and closest to the DS questionnaire administration were used in the present study.

**Dietary data.** Each year, participants were asked to complete three non-consecutive self-administered web-based 24 h dietary records, the days for which are randomly assigned during a 2-week period (2 d during the week and 1 d during the weekend). All foods and beverages consumed at breakfast, lunch, dinner and at all other occasions were recorded. For foods with potentially high nutrient variability, participants were also asked to provide the brand name. Participants were asked to estimate the portion size for each reported food and beverage item using a validated photograph booklet<sup>(36)</sup>. These photographs represented more than 250 foods (corresponding to about 1000 generic food items) in three different portion sizes. Along with the two intermediate and two extreme quantities, participants had seven choices of amounts. Daily dietary intakes of energy and nutrients were then calculated using the NutriNet-Santé food composition table<sup>(37)</sup>, which includes more than 2500 different foods. Dietary records from the year closest to the DS questionnaire administration (i.e. 2013 or 2014) were used in dietary data analyses.



### Statistical analyses

Proportions of DS users (i.e. at least one DS taken after cancer diagnosis) and type of and motivation for DS use were calculated overall and also by sex and main cancer sites (breast and prostate) in a cross-sectional design. For each DS reported in the study, circumstances of DS purchase, duration of use and communication with a physician about this use were described.

DS users and non-users were compared by age and sex-adjusted unconditional logistic regression analyses regarding their sociodemographic, anthropometric and lifestyle characteristics (sex, age, geographical region, marital status, number of children, educational level, smoking status, BMI and leisure-time physical activity). OR and their 95% CI were calculated.

Participants who provided at least two dietary records after cancer diagnosis (328 subjects excluded) and those who were

**Table 1.** Dietary supplement (DS) use in cancer survivors (*n* 1081, NutriNet-Santé cohort study, France, 2014)

(Number of subjects and percentages)

	All		Men ( <i>n</i> 350)		Women ( <i>n</i> 731)		Breast cancer ( <i>n</i> 382)		Prostate cancer ( <i>n</i> 168)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
DS use after cancer diagnosis* (yes)	556	51.4	101	28.9	455	62.2	261	68.3	48	28.6
Specific DS use in users†										
Vitamin D	251	45.1	34	33.7	217	47.7	128	48.9	19	39.6
Vitamin B <sub>6</sub>	209	37.6	40	39.6	169	37.1	94	35.9	19	39.6
Mg	184	33.1	35	34.7	149	32.7	85	32.4	21	43.8
Vitamin C	175	31.5	41	40.6	134	29.5	79	30.2	21	43.8
Zn	161	29.0	33	32.7	128	28.1	76	29.0	15	31.3
Vitamin E	159	28.6	34	33.7	125	27.5	72	27.5	18	37.5
Folate	145	26.1	32	31.7	113	24.8	60	22.9	15	31.3
Thiamin	138	24.8	31	30.7	107	23.5	60	22.9	16	33.3
Riboflavin	136	24.5	32	31.7	104	22.9	60	22.9	17	35.4
Niacin	134	24.1	30	29.7	104	22.9	61	23.3	16	33.3
Ca	122	21.9	21	20.8	101	22.2	53	20.2	13	27.1
Se	115	20.7	23	22.8	92	20.2	54	20.6	11	22.9
Fe	114	20.5	26	25.7	88	19.3	45	17.2	12	25.0
Pantothenic acid	108	19.4	22	21.8	86	18.9	50	19.1	11	22.9
Vitamin B <sub>12</sub>	91	16.4	25	24.8	66	14.5	32	12.2	11	22.9
Vitamin B <sub>8</sub>	91	16.4	18	17.8	73	16.0	38	14.5	7	14.6
Polyphenols	81	14.6	18	17.8	63	13.8	39	14.9	9	18.8
Acerola, guarana or cranberry	74	13.3	12	11.9	62	13.6	35	13.4	3	6.3
Fibre	72	12.9	15	14.9	57	12.5	43	16.4	8	16.7
Probiotics	71	12.8	9	8.9	62	13.6	42	16.0	2	4.2
Amino acids/proteins	68	12.2	13	12.9	55	12.1	32	12.2	3	6.3
Phyto-oestrogen	64	11.5	16	15.8	48	10.5	26	9.9	8	16.7
Retinol	61	11.0	9	8.9	52	11.4	30	11.5	4	8.3
<i>n</i> -3 Fatty acids	56	10.1	15	14.9	41	9.0	28	10.7	9	18.8
I	55	9.9	11	10.9	44	9.7	23	8.8	4	8.3
β-Carotene	46	8.3	9	8.9	37	8.1	19	7.3	4	8.3
P	43	7.7	9	8.9	34	7.5	21	8.0	3	6.3
<i>Desmodium</i>	40	7.2	2	2.0	38	8.4	28	10.7	1	2.1
Evening primrose, borage, or cod liver oil	33	5.9	1	1.0	32	7.0	23	8.8	1	2.1
Ginseng	33	5.9	8	7.9	25	5.5	9	3.4	2	4.2
Lutein	31	5.6	14	13.9	17	3.7	7	2.7	6	12.5
Zeaxanthin	13	2.3	6	5.9	7	1.5	3	1.1	3	6.3
Flaxseed oil	13	2.3	3	3.0	10	2.2	5	1.9	3	6.3
Red yeast rice	10	1.8	3	3.0	7	1.5	3	1.1	1	2.1
Lycopene	9	1.6	1	1.0	8	1.8	6	2.3	0	0.0
Echinacea	7	1.3	1	1.0	6	1.3	4	1.5	1	2.1
Vitamin K	5	0.9	2	2.0	3	0.7	0	0.0	2	4.2
Dehydroepiandrosterone	4	0.7	0	0.0	4	0.9	1	0.4	0	0.0
Phytoprogestagen	4	0.7	0	0.0	4	0.9	3	1.1	0	0.0
Fluoride	4	0.7	0	0.0	4	0.9	4	1.5	0	0.0
Alfalfa	3	0.5	0	0.0	3	0.7	3	1.1	0	0.0
Black cohosh	1	0.2	0	0.0	1	0.2	0	0.0	0	0.0
Other minerals‡	121	21.8	28	27.7	93	20.4	59	22.5	16	33.3
Other herbal supplements	34	6.1	7	6.9	27	5.9	12	4.6	4	8.3

\* At least one DS taken after cancer diagnosis.

† In decreasing order of frequency. Nutrients and other substances were consumed alone or in combination in a single DS. Percentages were calculated among overall DS users.

‡ K, Cu, Li, Mn, Cr and others.



not classified as under-reporters of energy intake according to the Black<sup>(38)</sup> criteria (eighty-five subjects excluded) were included in dietary data analyses (*n* 668). Most participants provided three 24 h dietary records, but 7% provided two records. The mean daily intake of dietary macro- and micro-nutrients from food only and from food and supplements were compared by unconditional logistic regression between DS users and non-users after adjustment for age, sex, number of 24 h dietary records and energy intake. The aim of the present analysis was to quantify the extent to which total nutrient intake increased when total intake from food and supplements was considered in comparison to intake from food only and which nutrients were more specifically impacted. For each nutrient, the proportion of total daily intake brought by DS was also estimated both in overall DS users and in DS users of the specific nutrient. The number of subjects who practised potentially harmful DS use was assessed. Such practices included: (1) use of  $\beta$ -carotene DS by smokers<sup>(5,10,11)</sup>; (2) the use of DS that should be avoided in certain cancer patients,

such as phyto-oestrogen use by hormone-dependent cancer patients<sup>(6,9)</sup>; and (3) the simultaneous use of DS (current use at the time of the DS and medication questionnaire) and drugs for which harmful interactions of moderate-to-major severity have been described in the literature<sup>(9,13–15)</sup>.

*P* < 0.05 was considered statistically significant. All tests were two-sided. Analyses were carried out with SAS software release 9.3 (SAS Institute, Inc.).

**Results**

A total of 1490 subjects developed an incident primary cancer between the beginning of the study and January 2014. Among them, 1081 answered the DS questionnaire (participation rate = 73%). The average age of cancer survivors was 60.2 (SD 10.9) years. Women constituted 68% of the sample. The main cancer types were breast (43%), followed by prostate (19%) and melanoma skin cancer (15%). The mean time between cancer diagnosis and administration of the DS questionnaire was 22.3 (SD 14.6) months.

**Table 2.** Reasons for dietary supplement (DS) use in cancer survivors (*n* 522, NutriNet-Santé study, 2014) (Number of subjects and percentages)

	All		Men ( <i>n</i> 97)		Women ( <i>n</i> 425)		Breast cancer ( <i>n</i> 246)		Prostate cancer ( <i>n</i> 46)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Reasons for DS use*										
Fight against cancer	249	47.7	41	42.3	208	48.9	140	56.9	20	43.5
Reduce adverse effects of cancer treatments	147	28.2	12	12.4	133	31.3	101	41.1	4	8.7
Fight against recurrences	72	13.8	15	15.5	57	13.4	41	16.7	8	17.4
Manage my disease	53	10.2	15	15.5	38	8.9	22	8.9	9	19.6
Reduce symptoms	45	8.6	8	8.2	37	8.7	27	11.0	3	6.5
Other reason related to cancer	42	8.0	14	14.4	37	8.7	18	7.3	2	4.3
Other health problems (other than cancer)	432	82.8	82	84.5	350	82.4	202	82.1	40	87.0
Strengthen immune system	281	53.8	56	57.7	225	52.9	130	52.8	30	65.2
Solve or fight against health problems	191	36.6	32	33.0	159	37.4	83	33.7	17	37.0
Prevent diseases	78	14.9	18	18.6	60	14.1	33	13.4	9	19.6
Other reason related to health problem	60	11.5	8	8.2	52	12.2	34	13.8	4	8.7
Improve my well-being	311	59.6	60	61.9	251	59.1	151	61.4	30	65.2
Overcome tiredness	202	38.7	41	42.3	161	37.9	92	37.4	20	43.5
Counter stress	67	12.8	7	7.2	60	14.1	29	11.8	3	6.5
Sleeping	54	10.3	3	3.1	51	12.0	31	12.6	1	2.2
Relieve female disorders related to menopause	45	8.6	0	0.0	45	10.6	30	12.2	0	0.0
Digestion, intestinal comfort	31	5.9	6	6.2	27	6.4	14	5.7	2	4.3
Circulation	23	4.4	5	5.2	18	4.2	9	3.7	3	6.5
Relieve female disorders related to premenstrual syndrome	2	0.4	0	0.0	2	0.5	1	0.4	0	0.0
Other reason related to the well-being	82	15.7	19	19.6	63	14.8	39	15.9	10	21.7
Fill in special needs	178	34.1	44	45.4	134	31.5	78	31.7	25	54.3
Compensate inadequate dietary intake associated with a restrictive diet	75	14.4	21	21.6	54	12.7	30	12.2	12	26.1
Compensate dietary intake perceived as inadequate (without restrictive diet)	65	12.5	10	10.3	55	12.9	33	13.4	8	17.4
Fill in special needs related to sport practice	47	9.0	17	17.5	30	7.1	19	7.7	10	21.7
Fill in special needs related to pregnancy	4	0.8	0	0.0	4	0.9	0	0.0	0	0.0
Improve my appearance and performance	221	42.3	48	49.5	173	40.7	111	45.1	27	58.7
Age well	131	25.1	38	39.2	93	21.9	54	22.0	24	52.2
Beauty	75	14.4	6	6.2	69	16.2	46	18.7	2	4.3
Improve intellectual performance	31	5.9	7	7.2	24	5.6	17	6.9	3	6.5
Stay young	12	2.3	8	8.2	4	0.9	3	1.2	4	8.7
Lose weight	10	1.9	1	1.0	9	2.1	6	2.4	0	0.0
Act on my silhouette	10	1.9	0	0.0	10	2.4	6	2.4	0	0.0
Improve sexual performance	1	0.2	1	1.0	0	0.0	0	0.0	0	0.0
Put on weight	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other reason related to my appearance or performance	30	5.7	4	4.1	26	6.1	15	6.1	2	4.3

\* At least one DS taken after cancer diagnosis. Data regarding reasons for DS use were missing for thirty-four DS users. Several answers were possible.

### Overall and specific dietary supplement use

DS use by sex and among breast and prostate cancer survivors is presented in Table 1. 62% of women (*n* 455) and 29% of men (*n* 101) reported using at least one DS after cancer diagnosis (*n* 556 in all): 442 were current users (at the time of the DS questionnaire), and 114 had taken DS since their cancer diagnosis but were not currently using DS. In current users, the number of DS taken simultaneously was 1, 2 or ≥3 in 52, 24 and 24% of the subjects, respectively. The mean number of DS taken was 1.9 (SD 1.4). Vitamin D, vitamin B<sub>6</sub>, Mg and vitamin C were the most frequently used DS nutrients. After cancer diagnosis, 14% of subjects started DS use, 9% kept using DS but modified the types of DS used and 4% stopped using DS (data not tabulated).

### Motivations for dietary supplement use, circumstances of purchase and involvement of attending physicians

The main stated reasons for DS use included: to reduce the adverse effects of cancer treatments (28.2%), to decrease the risk of cancer recurrence (13.8%), to strengthen the immune system (54%), and to overcome tiredness (39%) (Table 2, several answers possible). Similar motivations were reported by men and women and for breast and prostate cancer patients.

Among the 1140 DS reported by the participants, only about half of them (54%) were taken following medical prescription or advice (Table 3). Medical prescription or advice was higher for vitamin D DS (81%), medium for many vitamins and minerals (e.g. 43% for vitamin C and Mg and 47% for vitamin B<sub>6</sub>) and lower for herbal/natural DS (36% for acerola/guarana and 24% for phyto-oestrogen DS) (data not tabulated). Among the 1140 DS reported, 56% were used for more than 1 year. For 35% of reported DS, participants did not inform any of their attending physicians (general practitioner, oncologist or other) about their use. The main reason cited for this was that physicians did not ask their patients about their DS use (86%).

### Sociodemographic, lifestyle and anthropometric correlates of dietary supplement use

As compared to non-users (Table 4), DS users were more likely to be women (*P*<0.0001) those with higher educational levels (*P*=0.0001), never smokers (*P*=0.03) and those with a normal weight (*P*=0.0005).

### Dietary correlates of dietary supplement use and its contribution to nutrient intake

When considering food intake only (Table 5), DS users already had significantly higher intakes of fibre, vitamins B<sub>6</sub>,

**Table 3.** Circumstances of purchase, duration of use, and communication with the attending physician for the 1140 dietary supplements (DS) reported by cancer survivors (NutriNet-Santé cohort study, France, 2014)

(Number of subjects and percentages)

	Number of DS ( <i>n</i> 1140)	%
Circumstances of DS purchase*		
On medical prescription	451	39.6
On medical advice (without prescription)	168	14.7
Discovered the DS in-store by themselves	141	12.4
On the advice of a pharmacist	111	9.7
On the advice of a friend/family member	105	9.2
On the advice of another health professional	64	5.6
Heard of the DS from the media (television, magazine, etc.)	47	4.1
Heard of the DS from a book	46	4.0
Saw an advertisement	31	2.7
On the advice of a dietician	25	2.2
On the advice of another patient	20	1.8
On advice received in-store (except chemistry)	12	1.1
On the advice of a physical activity professional	8	0.7
Other circumstances	40	3.5
Duration of DS use (years)		
<1	506	44.4
1–2	283	24.8
3–5	210	18.5
5–10	86	7.5
>10	55	4.8
Have you informed one of your physicians† about this DS use?		
Yes	742	65.1
No	398	34.9
Reasons for not informing the physician‡		
He did not ask	343	86.2
He does not need to know	85	21.4
He could not understand	41	10.3
He would disapprove	17	4.3

\* Several answers were possible.

† General practitioner, oncologist or other attending physician.

‡ Among the 398 DS for which participants answered 'no' to the previous question. Several answers were possible.



**Table 4.** Sociodemographic, lifestyle and behavioural correlates of dietary supplement (DS) use in cancer survivors (*n* 1081, NutriNet-Santé cohort study, France, 2014)

(Number of subjects, percentages, odds ratios and 95% confidence intervals)

	All ( <i>n</i> 1081)		Percentage of DS users in each category* ( <i>n</i> 524)		Age and sex adjusted logistic regression analyses		
	<i>n</i>	%	<i>n</i>	%	OR	95% CI	<i>P</i>
Sex							<0.0001
Male	350	32.38	101	28.9	1.00		
Female	731	67.62	455	62.2	4.24	3.15, 5.71	
Age (years)							0.2
<55	306	28.31	170	55.6	1.00		
55–65	387	35.80	215	55.6	1.32	0.96, 1.81	
>65	388	35.89	171	44.1	1.17	0.83, 1.64	
Geographical region							0.9
Paris suburb	236	21.83	125	53.0	1.00		
North-North East	147	13.60	70	47.6	0.84	0.55, 1.30	
North-West	194	17.95	94	48.5	0.85	0.57, 1.27	
South-West	122	11.29	67	54.9	1.07	0.68, 1.70	
Centre	229	21.18	123	53.7	1.02	0.69, 1.49	
South-East	146	13.51	73	50.0	0.97	0.63, 1.50	
Others†	7	0.65	4	57.1	1.48	0.29, 7.43	
Marital status							0.8
Married or with partner	802	74.19	394	49.1	1.00		
Divorced/separated/widowed	189	17.48	108	57.1	1.10	0.78, 1.54	
Single	90	8.33	54	60.0	1.14	0.72, 1.82	
Children							0.09
Yes	367	33.95	176	48.0	1.00		
No	714	66.05	380	53.2	0.79	0.61, 1.04	
Education							0.0001
≤12 years of schooling	468	43.29	207	44.2	1.00		
>12 years of schooling	613	56.71	349	56.9	1.66	1.29, 2.15	
Smoking status							0.03
Never smoker	436	40.33	249	57.1	1.00		
Former smoker	523	48.38	255	48.8	0.57	0.37, 0.87	
Current smoker	122	11.29	52	42.6	0.90	0.68, 1.18	
BMI (kg/m <sup>2</sup> )							0.0005
Normal weight (18.5–24.9)	620	57.35	364	58.7	1.00		
Underweight (<18.5)	28	2.59	17	60.7	0.75	0.34, 1.64	
Overweight and obese (≥25)	433	40.06	175	40.4	0.59	0.45, 0.77	
Leisure physical activity‡							0.2
High	350	39.64	167	47.7	1.00		
Moderate	328	37.15	185	56.4	1.31	0.95, 1.81	
Low	205	23.22	107	52.2	1.12	0.77, 1.62	

\* At least one DS taken after cancer diagnosis.

† Overseas departments/territories.

‡ As measures by the international physical activity questionnaire. Because of missing values, the proportions of subjects were calculated on 883 participants (459 DS users and 424 non-users).

B<sub>9</sub> and C, Fe, Mg, K and Zn. When considering total intake (food + DS), DS users additionally had higher intakes of thiamin, riboflavin, niacin, pantothenic acid, vitamins D and E and Ca compared to non-users.

The contribution of DS to total nutrient intake was very high for some nutrients: in DS users of the specific nutrient, DS represented more than half of the total daily intakes for vitamins D (89%), B<sub>6</sub> (68%), E (68%) and B<sub>12</sub> (50%) and more than one-third of the total daily intake for fibre, thiamin, pantothenic acid, folate, retinol, vitamin C and Ca.

#### Potentially harmful dietary supplement use practices

Among the 442 DS current users (i.e. participants who were using DS at the time of the DS and medication questionnaire), eighty-one (18%) reported DS practices that were contraindicated

because of potential for adverse effects documented in the literature. Such practices are listed in Table 6 (one patient may cumulate several of these practices): thirty participants with smoking history (six current and twenty-four former smokers) used β-carotene DS, forty-four participants used DS that were contraindicated for specific cancer sites and thirty-nine participants simultaneously used DS and drugs for which a drug–nutrient interaction of moderate-to-major severity would be predicted.

#### Discussion

DS use was widespread in the present large sample of French cancer patients or survivors (29% of men and 62% of women). These proportions were lower than those observed in various American studies (50 to 81% DS users)<sup>(16,18,39)</sup>

**Table 5.** Comparison of daily dietary energy and nutrient intakes from food only and from food and dietary supplements (DS), between DS users (*n* 270) and non-users (*n* 398) among cancer survivors (NutriNet-Santé cohort study, France, 2014)\*

(Mean values, standard errors, number of subjects and percentages)

	Food only					Food + supplements					
	Non-users		Users		<i>P</i> †	Overall DS users			Specific DS users		
	Mean daily nutrient intake	SE	Mean daily nutrient intake	SE		Mean daily nutrient intake	SE	<i>P</i> †	% from DS	<i>n</i>	% from DS
Energy					0.4					270	
kcal	2096.7	37.8	2129.8	43.4		2133.8	43.4		0.2		0.2
kJ	8773	158.2	8911.1	181.6		8927.8	181.6		0.8		0.8
Alcohol (g)‡	12.2	1.1	11.1	1.2	0.3	11.1	1.2	0.3	0.0	3	18.6
Total carbohydrates (g)	192.4	3.0	193.6	3.4	0.7	193.9	3.4	0.6	0.2	91	0.5
Simple carbohydrates (g)	88.9	2.4	92.3	2.7	0.1	92.3	2.7	0.1	0.0	45	0.3
Starch (g)	102.9	2.4	100.6	2.8	0.3	100.6	2.8	0.3	0.0	0	0.0
Fibre (g)	19.3	0.6	21.3	0.6	0.0002	24.9	1.2	0.0001	14.5	42	38.0
Proteins (g)	85.3	1.2	85.7	1.4	0.8	87.8	2.0	0.1	2.4	79	11.1
Total lipids (g)	82.2	1.2	82.3	1.4	0.9	82.4	1.4	0.9	0.1	84	0.1
SFA (g)	32.6	0.7	31.9	0.8	0.3	31.9	0.8	0.3	0.0	44	0.0
MUFA (g)	31.6	0.6	32.2	0.7	0.2	32.2	0.7	0.3	0.0	13	0.0
PUFA (g)	11.4	0.3	11.7	0.4	0.4	11.7	0.4	0.3	0.0	65	3.3
Thiamin (mg)	1.2	0.0	1.2	0.0	0.5	1.4	0.1	<0.0001	14.3	97	36.8
Riboflavin (mg)	1.9	0.0	1.9	0.1	0.9	2.1	0.1	0.02	9.5	96	26.9
Niacin (mg)	20.7	0.5	21.3	0.5	0.2	23.1	0.6	0.0001	7.8	97	22.8
Pantothenic acid (mg)	5.7	0.1	5.8	0.1	0.3	6.5	0.2	<0.0001	10.8	80	34.1
Vitamin B <sub>6</sub> (mg)	1.8	0.0	2.0	0.0	0.001	3.6	0.8	<0.0001	44.4	151	68.3
Folate (µg)	335.2	9.4	354.6	10.8	0.03	468.7	21.8	<0.0001	24.3	110	37.9
Vitamin B <sub>12</sub> (µg)	7.5	0.5	7.2	0.6	0.6	8.3	1.1	0.4	13.3	65	50.0
Retinol (µg)	602.8	76.9	554.9	88.4	0.5	610.7	92.0	0.9	9.1	45	41.5
β-Carotene (µg)	3881.8	242.5	4087.2	278.9	0.4	4219.9	291.8	0.1	3.1	27	32.8
Vitamin C (mg)	115.6	7.7	132.4	8.9	0.03	156.9	10.6	<0.0001	15.6	123	40.4
Vitamin D (µg)	3.1	0.2	3.4	0.3	0.2	15.9	3.0	<0.0001	78.6	205	89.4
Vitamin E (µg)	12.5	0.4	12.8	0.4	0.4	19.8	4.1	<0.0001	35.4	113	67.6
Na (mg)	2903.5	65.6	2928.1	75.4	0.7	2929	75.6	0.7	0.0	54	0.6
Ca (mg)	907.8	22.5	923.2	25.8	0.4	1112.9	152.6	<0.0001	17.0	102	49.3
Fe (mg)	13.4	0.3	14.9	0.4	<0.0001	15.9	0.5	<0.0001	6.3	84	20.4
Mg (mg)	337.3	7.9	365.8	9.1	0.0002	389.1	10.6	<0.0001	6.0	123	15.1
P (mg)	1320.8	27.1	1353.7	24.2	0.1	1354	24.2	0.1	0.0	33	2.1
K (mg)	3229.9	59.5	3411.3	68.4	0.002	3416.1	68.5	0.001	0.1	33	2.0
Zn (mg)	11.3	0.2	12.0	0.3	0.005	13.0	0.3	<0.0001	7.7	117	26.1

Dietary supplement use among cancer survivors

\* In subjects with at least one 24 h dietary record after cancer diagnosis, normo-energy reporters. DS users were defined as subjects who used at least two DS after cancer diagnosis.

† Logistic regression analysis (performed to derive the *P*-value for the comparison between DS users and non-users) were adjusted for sex, age, number of 24 h dietary records and energy intake.

‡ Very small amounts of alcohol can be found in some DS or medicinal products as excipients (not as main active substance).

**Table 6.** Dietary supplement (DS) use that may convey adverse effects in cancer survivors (NutriNet-Santé cohort study, France, 2014) (Number of subjects)

	<i>n</i>
Use of $\beta$ -carotene DS in smokers	
$\beta$ -carotene/current smokers	6
$\beta$ -carotene/former smokers	24
Use of DS that should be avoided in	
hormone-dependent cancer patients	
Phyto-oestrogens/breast cancer	26
Chasteberry/breast cancer	3
Dehydroepiandrosterone/breast cancer	1
Phyto-oestrogens/ovarian or endometrial cancers	5
Phyto-oestrogens/prostate cancer	8
Saw palmetto/prostate cancer	1
Simultaneous use of DS and medications that may lead to moderate-to-severe harmful interactions	
Vitamin E/anticoagulant/antiplatelet agents	10
Niacin/statins	7
Safflower/anticoagulant/antiplatelet agents	3
Flaxseed/antiplatelet agents	3
Turmeric/anticoagulant/antiplatelet agents	2
K/spironolactone	2
Echinacea/antiplatelet agents	2
Ginseng/anticoagulant/antiplatelet agents	2
<i>Ginkgo biloba</i> /anticoagulant agents	1
Glucosamin/antiplatelet agents	1
K/captopril	1
Red yeast rice/anti-cholesterol drugs	1
Valerian/tamoxifen	1
Cinchona/anticoagulant agents	1
Milk thistle/anticoagulant agents	1
Soya/anticoagulant agents	1

but were closer to figures observed in other European countries<sup>(23,24,28,40)</sup>. As suggested earlier<sup>(41,42)</sup>, cancer diagnosis may have influenced DS use. Indeed, the present findings showed that 28% of participants started, stopped or modified their DS use after cancer diagnosis. Further research into patients' beliefs regarding DS and cancer is needed to better understand these changes.

As observed in the NutriNet-Santé cohort for the general population<sup>(43)</sup>, vitamins B<sub>6</sub> and C and Mg DS were among the most frequently consumed DS. In addition, in the present population of cancer survivors, vitamin D emerged as the most frequent supplementation (used by 45% of DS users). This high prevalence of vitamin D DS use, especially in women, was consistent with prior investigations conducted in the United States<sup>(20,41,44)</sup>. Indeed, several anti-cancer treatments, such as aromatase inhibitors, which are used to treat postmenopausal breast cancers and androgen-deprivation therapy, which is used to treat prostate cancer<sup>(45)</sup>, may induce bone loss and thus justify vitamin D supplementation.

Cancer itself and its consequences appeared as a strong motivation for DS use. Another frequently cited motivation was to 'strengthen immune system', which is in line with previous studies<sup>(16,18)</sup> and with the fact that the immune system is often altered by chemotherapy and radiotherapy treatments. To 'overcome tiredness' was also among the main motivations for DS use in the NutriNet-Santé general cohort<sup>(43)</sup>, and this was in line with the frequent use of vitamins B<sub>6</sub> and C and Mg DS, which are recognised by the European Food Safety Authorities for their anti-fatigue properties<sup>(46–48)</sup>.

About 45% of DS use corresponded to self-medication, and 55% were taken following medical prescription or advice. This proportion varied across DS types. Whereas some types of self-medicated DS should be avoided by cancer survivors, others may truly be useful if consumed under medical supervision. For instance, this is the case for vitamin D, as discussed earlier. We consistently observed that the proportion of medical prescription or advice was higher for this nutrient (81%).

A substantial proportion (35%) of DS use was not discussed with a physician. Although this proportion was lower than that found in US studies (56–68%)<sup>(16)</sup>, it remains a concern because of the potential interactions between DS and adjuvant therapy or other medications<sup>(9,13,14)</sup>. The main reason why patients did not inform their physician was simply that the latter did not ask about DS use by their patient, which is in line with the literature<sup>(49)</sup>. This suggests that physicians may not be fully aware of the medical importance of knowing whether their cancer patients are using DS. It has also been hypothesised that the perception of physician neutrality or indifference, or possibly even a fear of physician opposition, are reasons why patients may be hesitant to communicate with their physicians about DS use<sup>(16)</sup>. Another possibility is limited physician time during medical consultations.

Previous studies of DS use in cancer survivors in other countries also found that female sex<sup>(18,39,44)</sup>, higher education<sup>(16,18,39,50)</sup>, non-smoking<sup>(17)</sup> and lower BMI<sup>(17,39)</sup> were associated with DS use. These factors have also been associated with DS use in the general French population<sup>(43,51)</sup>. Although some studies have identified older age<sup>(39,44)</sup> as a correlate of DS use, it was not a significant predictor in the present study's population. Likewise, a review on vitamin and mineral supplement use among US cancer survivors<sup>(16)</sup> pointed out that DS use may differ by the type of cancer, but we did not find significant association in the present population between main cancer types after age and sex adjustment (data not shown).

As it has been observed in the general population<sup>(43)</sup>, DS use was associated with a healthier diet that already includes higher intakes of fibre and several vitamins and minerals from food only. The high contribution of DS to total nutrient intake highlights the importance of taking this source of intake into consideration both in clinical practice and in nutritional epidemiological studies. Few studies have provided detailed information about total micronutrient intake from food and supplements in cancer survivors<sup>(19,52)</sup>. Compared to DS users in the American Women's Healthy Eating and Living Study<sup>(19)</sup>, DS users in the present study had a lower total daily intake for almost all micronutrients, except for vitamin D, folate, Ca and Mg, which were similar in intake amount. These differences may notably be explained by the variability of DS formulations between the United States<sup>(53)</sup> and Europe<sup>(54)</sup>.

Several interactions between herbal or vitamin/mineral DS and drugs that may lead to moderate-to-major adverse effects have been well documented<sup>(9,13–15)</sup>. As recommended by official authorities, some DS should also be avoided by certain cancer patients, such as phyto-oestrogens in oestrogen receptor-positive cancers<sup>(6,9,14)</sup>. Another potentially harmful



practice is the use of  $\beta$ -carotene DS, which is recognised for its association with increased lung and gastric cancers risk<sup>(5,10,55)</sup> in current smokers but also maybe in former smokers<sup>(11)</sup>. A relatively high proportion of DS users in the present study (18%) were concerned by such potentially harmful practices. Potentially problematic drug–nutrient interactions reported in the present study mainly concerned anticoagulants/antiplatelet agents and not specifically anti-cancer treatments, which may be explained by the fact that the DS questionnaire was administered 22 months after diagnosis on average.

The strengths of the present study are that it included a large number of cancer cases, detailed data about DS use (including precise doses and composition) and its dietary and lifestyle correlates, information about drugs taken simultaneously, and it was original in a French/European context.

The main limitation was that the present study's population may not be representative of all French male and female cancer survivors, given that the NutriNet-Santé study involved volunteers who accepted to participate in a cohort on nutrition and health. Compared to national estimates<sup>(56,57)</sup>, the NutriNet-Santé study included more women than men and more individuals who belong to higher socio-professional categories. In addition, some eligible cancer survivors did not answer the DS questionnaire. Compared to respondents, non-respondents were more likely to be women, to have more children and to have cancers other than those mainly represented in the cohort ( $P < 0.0001$ , data not shown). However, response rates to the DS questionnaire was high (73%) compared to similar epidemiological studies<sup>(18,21,42,50,58)</sup>. In addition, because the DS questionnaire was administered 22 months after diagnosis on average, a recall bias may have occurred for DS that were not currently being taken by the participants. Finally, although the sample size was reasonably large overall, only the main cancer types (i.e. breast and prostate) could be analysed, and other types with lower incidence could not be investigated separately.

In conclusion, the present study provides new and detailed information about DS use and its correlates in a large sample of French cancer survivors. The findings suggest that DS use was widespread in the present population and substantially contributed to total nutrient intake, with 14% of subjects initiating DS use after diagnosis. DS users had an overall healthier profile (in terms of diet, smoking status and BMI) than non-users. The present study highlighted the absence of communication about DS use between patients and healthcare professionals (for 35% of reported DS) and the importance of self-medication (45%). Worryingly, a substantial proportion of potentially harmful practices were detected (in 18% of DS users), including the simultaneous use of vitamin E and anticoagulant/antiplatelet agents, the use of  $\beta$ -carotene by smokers and the use of phyto-oestrogens by hormone-dependent cancer patients. Physicians should be encouraged to more routinely discuss DS use with their cancer patients and to warn them about potential adverse effects. Finally, given the widespread use of DS in cancer patients and survivors, further etiological research is needed to better elucidate its impact on cancer prognosis, the risk of recurrence and the risk of second cancer.

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