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ORIGINAL CONTRIBUTION

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Supplement use and mortality: the SENECA study

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Abstract *Background* It is hypothesis that in relatively healthy older people supplement usage can be consider as healthy life style habit and as such can positively influence longevity. *Aim of the study* To determine whether supplement use was associated with all-cause mortality in the participants of the SENECA study. *Methods* Baseline measurements were carried out in 1988/1989 among 75 to 80-year-old people living in 15 European small towns. All-cause mortality was followed up to April 30, 1999. Data from 920 men and 980 women who were ischemic heart diseases-, stroke- and cancer-free at baseline were included. The multivariate adjusted (for sex, age, years of education, physical activity, BMI, chronic diseases, Mediterranean Diet Score, alcohol use and the place of living) hazard ratio (HRs) and 95% confidence intervals (CIs) of mortality by use of any type of nutrient supplement and by particular nutrient supplement use were estimated by Cox proportional hazards regression models. *Results* At baseline, 13% of participants used nutritional supplements, 19% of subjects were smokers. During 10 years of follow-up 445 men and 252 women died. Among non-smokers no significant associations between total supplement use and particular nutrient supplement use were observed. Among smokers use of any type of supplements (Multivariate HR: 1.52; 95%CI: 1.02–2.28), use of vitamin B_1 (Multivariate HR: 1.57; 95%CI: 1.00–2.48) and vitamin B_2 supplements (Multivariate HR: 1.60; 95%CI: 1.00–2.56) were associated with a significantly higher risk of all-cause mortality. The similar tendencies were observed among vitamin B_6 and vitamin C supplement users who were smokers. *Conclusions* Among smokers, participants of the SENECA study, supplement use increased all-cause mortality risk.

Key words elderly – Europe – supplement use – mortality – smoking

Introduction

Despite the wide use of vitamin and mineral supplements in different populations, the effects of such a practice on health have not been well defined [20]. Several studies [16, 17, 19] reported that supplement usage is beneficial for primary and secondary prevention of some diseases and improves quality of life. Holmquist et al. [17] study indicated that using of low

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doses of multivitamin supplements was relevant to lowering risk of myocardial infraction. Jacobs et al. [18, 19] observed significant decreased the risk of stomach cancer mortality among vitamin C users and colon cancer mortality among multivitamin supplements users. In contrast other studies [15, 18, 20, 28, 34 and 41] have failed to demonstrate the positive effect of supplementation in preventing age-related diseases.

The baseline round of the Survey in Europe on Nutrition and the Elderly, a Concerted Action (SENECA) revealed, on the basis of the blood analyses, a significant prevalence of deficiency for several nutrients including vitamin B_6 (up to 50% of subjects), vitamin B_{12} (2–10%) and vitamin E (1–21%) among older people from small European towns [13]. To counteract low nutritional status only 13% of respondents reported having taken nutritional supplements [1]. The aim of this paper was to determine whether the use of supplements was associated with health benefits, measured as lowering all-causes mortality in the participants of SENECA study.

Subjects and methods

Study population

Data presented in this paper were collected at baseline (1988/1989) and final (1999) round of the SENECA survey. The population under study consisted of randomly selected, born between 1913 and 1918, habitants of 15 small towns in 11 European countries: Hamme (B), Roskilde (DK), Haguenau and Romans (F), Anogia and Archanes (GR), Monor (H), Padua, Fara Sabina, Magliano Sabina and Poggio Mirteto (I), Culemborg (NL), Vila Franca de Xira (P), Betanzos (E), Yverdon-les-Bains, Burgdorf and Bellinzona (CH), Marki (PL) [11].

In view of a poor prognosis and the high risk of death, subjects who suffered from ischemic heart diseases (376 subjects), stroke (63 subjects) and malignancy (46 subjects) were excluded. Finally, the analyses included 920 men and 980 women.

Data collection

Data were collected by interview at the participants' homes according to a standardised protocol [10]. Information about use of pharmaceutical preparations containing vitamins or/and minerals was collected with the question: "Do you use medicines, vitamins/minerals (tablets or injections) or tonics? If yes, please show them." Participants were also asked about daily doses. Having data on the composition of supplements available for subjects the intake of 9 vitamins, calcium and iron were calculated on the local level.

Modified dietary history method was used to collect information about food consumption during the month before the interview. This method was validated against a 3-day weight record method in a subsample of 82 elderly subjects from 11 participating centres. Pearson's correlation coefficient for nutrient intake varied from 0.18 (vitamin A) to 0.79 (water) with a median coefficient of 0.58 [29]. The quality of diet was assessed by modified Mediterranean Diet Score (MDS) which comprised: ratio of MUFA to SFA; intake of: legumes, nuts, and seeds; cereal products and grains; fruits; vegetables and potatoes; meat and meat products; dairy products; and fish. The diet score varied from 0 (low quality diet) to 8 (high quality diet) [22].

Vorrips questionnaire was used to assess habitual physical activities of the last year. Items on household activities were estimated from very active to inactive (4–5 possible ratings). Sports and other activities were determined as type of activity; hours per day or week spend on it, and the period of the year in which the activity was normally performed. The value of Voorrips Score was calculated on bases on the net energetic cost of particular activities [40].

Non-smoking subjects were defined as never smoking or non-smoking since more than 15 years ago at baseline round of the study. Data about mortality were collected up to April 30, 1999.

Statistical analysis

All statistical analyses were done using the SPSS software (v.11.0). Because there were statistically significant interactions between smoking status of participants and use of any type of nutrient supplements as well as use of particular nutrient supplements, all the analyses were carried out separately for smokers and non-smokers.

The unadjusted Kaplan–Meier curves by supplement use and smoking status were fitted, and log-rank test was used to compare survival distribution between supplement users and non-users. Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of mortality for users of any type of nutrient supplements as well as for users of particular nutrient supplements (vitamin B_1, B_2, B_6, B_{12}, C, A, D, E, folic acid, calcium and iron, separately) versus non-users. Multivariate HRs estimates and 95% CIs were adjusted for sex (men, women), age (continuous variable), years of education (continuous variable), physical activity (Voorrips Score: ≤8 points, >8 points),

Table 1 Description of the population (baseline study)

	Men (N = 920)	Women (N = 980)
Age (years) means ± SD	73.3 ± 1.8	73.2 ± 1.9
Education (years) means ± SD	8.6 ± 4.1	7.5 ± 3.6
Self-perceived health (%)		
Very poor and poor	6.7	10.8
Fair	24.7	31.5
Good and very good	68.3	56.7
Chronic disease (%)	64.5	76.3
Mediterranean diet score, modified (%)		
≤4 points	60.8	59.9
>4 points	39.2	40.1
Smoking (%)	32.0	7.5
Alcohol use (%)	79.6	49.3
Supplement use (%)	10.9	14.8
Voorrips score (points) means ± SD	18.5 ± 13.4	11.8 ± 9.5
Body mass index (kg/m^2) means ± SD	26.6 ± 3.8	27.0 ± 4.7
<20 (%)	3.2	5.4
20–25 (%)	30.5	30.0
25–30 (%)	48.9	39.4
>30 (%)	17.4	25.2
Albumin (g/l) means ± SD	41.9 ± 3.2	41.6 ± 3.0

BMI (≤25 kg/m^2, >25 kg/m^2), chronic diseases (yes, no), modified MDS (≤4 points, >4 points), alcohol use (non-consumption, consumption) and the place of living (latitude ≤47°North, >47°North). The statistical significance was considered at $P < 0.05$.

Results

Characteristics of the cohort

At the beginning of the study the mean age of the subjects was 73.3 ± 1.8 years (Table 1). During the baseline study, 11% of men and 15% of women used supplements, 32% of men and 8% of women were smokers. Fourteen percent of smoking men and 5% of women smoked more then 25 cigarettes or other tobaccos per day, 26% of smoking men and 16% of women smoked 15–24 cigarettes, 26% men and 35% of women smoked 5–14 cigarettes and other men and women smoked ≤4 cigarettes. A high percentage of study population suffered from chronic diseases (65% of men and 76% of women) as well as overweight and obesity (49 and 17% of men and 39 and 25% of women, respectively). The diets of approximately 40% of participants were scored above four points of a modified MDS.

During 10 years of SENECA study 445 men and 252 women died.

Intake of vitamins and minerals from supplements in relation to smoking status

A higher percentage of smoking men and smoking women used supplements (14.4 and 32.9%, respectively) in comparison to non-smoking subjects (9.2 and 13.4%, respectively). Vitamins B_1, B_2 and B_6 and C were used most often among both, smokers and non-smokers, while folic acid and calcium supplements were used by a lower number of subjects (Table 2).

The median intake of vitamins and iron from supplements was in the range of recommendations for these nutrients while median doses of supplemental calcium were very low. A part of non-smokers subjects used large doses of iron, the 90th percentile of supplemental intake of this nutrient amounted 67 mg/day, what exceeded the upper intake level (25 g/day) proposed in Nordic Recommendations [30].

Table 2 Intake of vitamins and minerals from supplements in relation to smoking status

Nutrient in supplements	Supplement users							
	Non-smoking (N = 176)				Smoking (N = 66)			
	%N	Percentiles			%N	Percentiles		
		10	50	90		10	50	90
Vitamin B_1 (mg/d)[a]	57	1.2	2.0	63	71	1.0	2.0	20
Vitamin B_2 (mg/d)[a]	56	1.5	2.0	26	67	1.0	2.0	8
Vitamin B_6 (mg/d)[a]	60	0.8	2.0	36	69	0.5	2.0	10
Folic acid (μg/d)[a]	29	100	100	400	36	50	100	200
Vitamin B_{12} (μg/d)[a]	38	1.7	3.0	249	61	1.0	3.0	600
Vitamin C (mg/d)[a]	51	16	60	209	68	20	60	200
Vitamin A (μg/d)[a]	44	200	1,200	3,000	59	300	1,000	4,000
Vitamin D (μg/d)[a]	43	5	10	26	64	8	10	355
Vitamin E (mg/d)[a]	44	3	10	103	58	1	10	71
Calcium (mg/d)	35	3	162	1,000	23	5	97	700
Iron (mg/d)[a]	33	4	16	67	53	2.3	18	22

[a]Significant difference in prevalence of supplementation practice between non-smokers and smokers

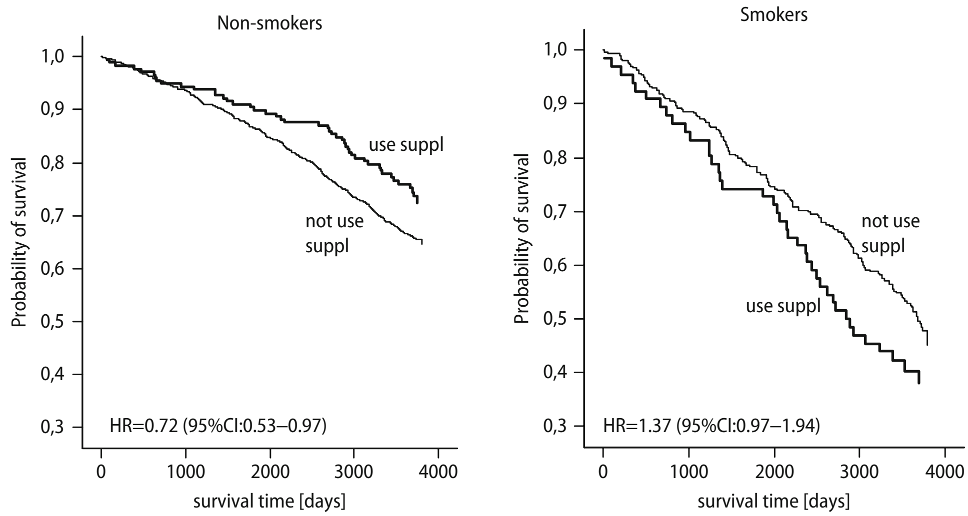

Fig. 1 The unadjusted Kaplan–Meier survival curves for subjects from SENECA's baseline study by supplement use and smoking status

Supplement use and mortality

Among non-smokers unadjusted hazard ratio was a statistically significantly lower (28%) among supplement users than among non-users (Figure 1). The similar tendencies were observed among users of vitamins B_1, B_2 and B_6 and calcium. In contrast, among smokers there were tendencies towards an increase in mortality among users of any type of supplements (37%) as well as among vitamin B_1, B_2, B_6 and vitamin C supplement users (43–47%) versus non-users.

After multivariate adjustments (Table 3), among non-smokers none of the differences in all-cause mortality related to total or particular nutrients supplement use were statistically significant. Whereas among smokers the multivariate-adjusted hazard ratio for subjects who used any type of nutrient supplements compare to those who did not use them was significantly higher (52%, $P = 0.04$), for vitamin B_1 and B_2 supplements users HRs were also higher (57 and 60%, respectively, $P = 0.05$). The similar tendencies were observed among smokers—vitamin B_6 and vitamin C supplement users.

Table 3 Hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality in SENECA-population by supplement use and smoking status unadjusted and adjusted for possible confounders

Users of nutrient supplements	Non-smoking (*N* = 1,527)		Smoking (*N* = 365)	
	HR	95% CI	HR	95% CI
Unadjusted				
Total[a]	0.72	0.53–0.97	1.37	0.97–1.94
Vitamin B_1	0.74	0.50–1.09	1.45	0.98–2.13
Vitamin B_2	0.74	0.45–1.02	1.44	0.96–2.15
Vitamin B_6	0.67	0.45–1.00	1.43	0.96–2.12
Folic acid	0.73	0.42–1.26	1.14	0.66–1.97
Vitamin B_{12}	0.97	0.62–1.49	1.25	0.82–1.92
Vitamin C	0.76	0.51–1.15	1.47	0.99–2.18
Vitamin A	0.75	0.48–1.16	1.21	0.78–1.87
Vitamin D	0.83	0.54–1.28	1.17	0.76–1.80
Vitamin E	0.86	0.56–1.30	1.13	0.72–1.78
Calcium	0.62	0.37–1.06	0.85	0.40–1.80
Iron	0.68	0.40–1.15	1.27	0.81–2.00
Adjusted[b]				
Total[a]	0.80	0.57–1.11	1.52	1.02–2.28
Vitamin B_1	0.80	0.52–1.23	1.57	1.00–2.48
Vitamin B_2	0.71	0.45–1.11	1.60	1.00–2.56
Vitamin B_6	0.71	0.46–1.09	1.52	0.96–2.42
Folic acid	0.77	0.42–1.42	1.19	0.64–2.20
Vitamin B_{12}	1.12	0.70–1.79	1.22	0.74–2.00
Vitamin C	0.71	0.45–1.13	1.55	0.97–2.46
Vitamin A	0.82	0.50–1.34	1.22	0.73–2.03
Vitamin D	0.91	0.57–1.46	1.27	0.77–2.11
Vitamin E	0.97	0.62–1.51	1.31	0.78–2.21
Calcium	0.72	0.41–1.26	0.81	0.33–2.00
Iron	0.85	0.49–1.49	1.34	0.79–2.27

[a] Users of any type of nutrient supplements
[b] Adjusted for sex, age, education, physical activity, body mass index, chronic diseases, Mediterranean Diet Score, alcohol use, latitude

Discussion

Our study shows that supplement use is associated with mortality differently in smoking and non-smoking elderly and provide no evidence of a beneficial effect of supplement use on the risk of mortality during 10 years follow-up among SENECA's population. Slight adverse effects were found in smoking subjects. In smoking subjects the supplement use (any type or vitamin B_1, and B_2) was associated with slight adverse effects.

Some meta-analysis of randomized controlled trials also showed no evidence of a protective effect of supplement use on mortality or morbidity [3, 5, 6, 8, 9]. No evidences of a protective effect were found in the case of antioxidant or B-group vitamin supplements on the progression of atherosclerosis [6] and antioxidant supplements on gastrointestinal cancer [5], of vitamin C and vitamin E supplements use on various type of cancer [9], as well as usage of vitamin A, C, E and folate supplements on prevention of lung cancer [8]. Moreover, Bjelakovic et al. [4] who analyzed 68 randomized trials with 232,606 participants showed that treatment with antioxidant vitamins may increase all-cause mortality.

However, observational and experimental studies reported also inverse association between supplement use and mortality. Slightly decreased risk of colon cancer mortality among multivitamin users was observed with stronger association among moderate to heavy alcohol users. At least 15 years of follow-up was required to see the benefit of supplement use [19]. Low doses of multivitamin supplements were associated with substantially lower risk of nonfatal myocardial infarction in Stockholm Heart Epidemiology Program [17]. The results of SU.VI.MAX study indicated that nutritional doses of a combination of vitamin C, vitamin E, beta-carotene, selenium and zinc might have a protective effect on mortality in apparently healthy men in the age of 45–60 years [16].

Similarly as in our study, the adverse effect of supplement use on survival among smokers was reported by others [24, 32, 38, 41]. The β-Carotene and Retinol Efficacy Trial (CARET) was stopped 21 months earlier than planned because after 4 years the relative risks of death from any cause, from lung cancer and from cardiovascular diseases were higher among subjects who received combination of β-carotene and vitamin A than among the placebo group [32].

Watkins et al. [41] showed that the mortality from all cancers was significantly higher among smoking men who used multivitamins alone (HR: 1.13, 95%CI: 1.05–1.23) or in combination with vitamin A, C or E (HR: 1.16, 95%CI: 1.06–1.23); whereas among subjects who had never or had formerly smoked and used supplements hazard ratios were significantly lower, i.e. 0.86 (95%CI: 0.74–0.99) and 0.90 (95%CI: 0.82–0.98), respectively.

Moreover, among the participants of the Finnish ATBC Cancer Prevention Study α-tocopherol supplementation increased the risk for adenomas (HR: 1.66, 95%CI: 1.19–2.32), whereas β-carotene supplementation had no effect on the risk (HR: 0.98, 95%CI: 0.71–1.35) [25].

The mechanisms of the adverse effect of supplemental vitamins are still not fully explained. Probably, they could be related to pro-oxidative role of antioxidants when their doses are too high or as the results of interactions with components of cigarette smoke. In our study the median intake of supplemental nutrients did not exceed significantly the recommended dietary intake among smokers, but the 90th percentile of intake exceeded three to ten times the RDA's for vitamin B_1, B_2, and C. High dose of those supplements probably had an adverse effect on health of participants who were smokers.

In humans different cellular markers of DNA damage were used to assess the pro-oxidative effects of vitamin C supplements in smokers. Welch et al. [42] observed a significant increase of 7-hydroxy-8-oxo-2′-deoxyguanosine concentrations after β-carotene supplementation in smokers, whereas in non-smokers the concentration of this marker decreased. Rehman et al. [36], who examined the effects of iron (14 mg/day) and vitamin C (either 60 or 260 mg/day) supplementation found that in subjects with higher initial level of plasma vitamin C total oxidative DNA damage in white blood cells significantly increased after supplementation. Whereas, in low plasma ascorbate subjects the supplementation was beneficial.

In clinical trial among smokers who regularly received 500 mg/day vitamin C a significant increase of plasma TBARS was shown, what indicated the increase of oxidative lipid damage [31].

In contrast, others studies were failed in founding the significant changes in DNA damage or LDL-lipid peroxidation after supplementation with vitamin C [2, 27], vitamin E [37], β-carotene [12, 35, 39] and vitamin combinations [33]. Moreover, also protective effect of supplement use on DNA damage was observed [7, 14, 23, 26].

Moreover, contrary to expectations high supplemental folate levels and folate intervention, after microscopic neoplastic foci are established in the colorectal mucosa, promote rather than suppress colorectal carcinogenesis. The results of animal studies suggest that folate possesses the dual modulators effect on carcinogenesis depending on the timing and dose of folate intervention. Folate deficiency has an inhibitory effect whereas folate supplementation has a promoting effect on progression of established neoplasms [21].

No data on the effect of B-group vitamins supplementation on mortality among smokers was found in the literature.

Data on vitamin/mineral supplement use presented in this paper were collected among free-living elderly, aged at the beginning of the study 70–75 years. At that time the prevalence of supplement use was rather small, i.e. 13%. Even the subjects were asked about current supplement use many of them were long-term users. Of the 1,043 participants who were reinterviewed in 1993 12% reported using supplements at baseline and after 5 years, 69% of participants reported not using supplements at either time. A potential limitation of this study was the change in classification of 19% of the respondents after 5 years from the beginning of the study, i.e. 5% gave up this practice and 14% became supplement users. Our reference group therefore included some participants who become users after 5 years of observation. Another limitation was related to a statistical significant interaction between supplements use and smoking status of the participants. Dividing subjects into smokers and non-smokers groups made the subgroups small in number of cases and decreased the power of analysis.

In summary, supplementation practice had no beneficial effect on mortality among 70 to 75-year-old European participants of SENECA population. Our results indicated that some supplements should be used with special cautiously, and further studies are necessary, which also would allow for explanation of the mechanisms of harmful effects of supplements among smoking subjects.

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