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High-dose vitamin C supplement use is associated with self-reported histories of breast cancer and other illnesses in the UK Women's Cohort Study

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Abstract

Objective: To determine whether frequent vitamin C supplement use is associated with healthier behaviours, and a history of cancer and other illnesses in UK women.
Design: The present cross-sectional analysis examines the odds of taking supplements containing vitamin C as recorded in 4 d food diaries, based on lifestyle characteristics and morbidity history self-reported by questionnaire.
Setting: A large national UK cohort study.
Subjects: A total of 12 453 women aged between 37 and 79 years.
Results: Women frequently taking supplements containing vitamin C, compared to those who did not, had healthier behaviours, including higher consumption of fruit and vegetables. Frequent high-dose vitamin C users (≥1000 mg) had a higher socio-economic status, visited alternative practitioners more often than family or private doctors, and were more likely to be ex-smokers and to drink little or no alcohol. Women who self-reported having had cancer (OR = 1·33, 95 % CI 1·00, 1·76) or specifically breast cancer (OR = 1·70, 95 % CI 1·14, 2·55), or reported a family history of cancer (OR = 1·16, 95 % CI 0·95, 1·41) or breast cancer (OR = 1·26, 95 % CI 1·01, 1·58) had increased odds of being frequent high-dose users after adjusting for sociodemographic and health behaviours. Women with personal or family histories of some cardiovascular or intestinal disorders were more likely to take supplements containing vitamin C, though not necessarily at high doses.
Conclusions: High-dose vitamin C intake by UK women was associated with healthier behaviours and a history of breast cancer, total cancer and other illnesses. Consequences of high-dose vitamin C supplement intake are not clear at the population level.

Keywords
Supplements
Vitamin C
Health status
Lifestyle behaviours

Despite lack of evidence of benefits[1,2], the intake of vitamin supplements reported by UK women increased from 17 % in 1986–1987 to 41 % reported in 2008–2009[3,4]. A recent UK survey showed that users are most likely to be women aged >55 years and of higher socio-economic status[5]. An analysis of the UK Women's Cohort Study (UKWCS) found that users were significantly more likely to lead healthier lifestyles: to be more physically active; have a lower alcohol intake; a lower BMI; and eat diets that met the recommended dietary intake[6]. Therefore, they were less likely to need supplements than non-users[6]. Further support for this 'inverse supplement hypothesis' has been found in the UK[4,7,8] and elsewhere[9–14]. Moreover, those classifying themselves as high-strength supplement users in a recent UK survey were particularly health conscious[5].

Vitamin C is one of the most commonly used supplements in the UK[5,15]. However, suggestions that it is able to reduce the incidence of colds have been unsubstantiated in randomised controlled trials[16]. Furthermore, despite some clear evidence of an association between plasma vitamin C levels and reduced mortality from all causes, from CVD and from IHD[17], there is limited evidence to suggest that vitamin C supplement use is associated with reduced risk of CVD or mortality[2,18–20].

Although general supplement use is particularly widespread in cancer survivors in the USA, with breast cancer survivors showing the highest use[21], no overall association between vitamin C supplement intake (≥150 mg) and prevalent cancer was found in the US Vitamins and Lifestyle (VITAL) cross-sectional study[22]. Furthermore, those with pre-existing diabetes, hypertension and CVD

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were less likely to use them[22]. However, a US study of women physicians showed those with pre-existing breast cancer were more likely to take vitamin C supplements than breast cancer-free women[10].

UK health-conscious women with prevalent cancer were also more likely to take any supplement than cancer-free women[15]; however, other pre-existing chronic diseases have been inversely associated with the intake of vitamins, minerals or antioxidants in a UK study combining men and women[7]. To the best of our knowledge, no study has examined the relationship between the intake of vitamin C supplements in UK women and lifestyle factors or personal or family history of morbidities. The main aim of the present study was to determine whether women in the UKWCS who reported having had cancer or reported a relative who had cancer were more likely to use vitamin C supplements than those who did not report these histories. Further aims of the present study were to determine whether vitamin C supplement use was associated with other morbidities and healthier behaviours.

Methods

UKWCS recruitment data were gathered between 1995 and 1998 from 35 367 women who completed a 217-item FFQ[23–25]. This national cohort, which was designed to compare disease incidence in vegetarians, fish-eaters and meat-eaters, consisted of mainly Caucasian, well-educated, middle-class, middle-aged, married women who were recruited via the World Cancer Research Fund (WCRF)[23]. At recruitment, 62 % of participants took some type of dietary supplement.

All the initial participants were re-contacted between 1999 and 2004, on average 4 years after recruitment; 12 453 (35 %) completed a follow-up health and lifestyle questionnaire and a 4 d food diary. For each day, the diaries requested supplement brand, name, amount taken and dosage of any supplement taken. This information was matched against a database of supplement descriptions and ingredient compositions obtained from product labels provided by participants, suppliers' websites or provided directly by the manufacturers. The average daily intake of vitamin C contained in all supplement types was calculated for the total number of diary days on which vitamin C was taken.

Using the STATA statistical software package version 10·0 (StataCorp., College Station, TX, USA), univariable logistic regression was applied to the follow-up data to determine which participant characteristics predicted frequent supplement intake in two different classifications of users: those taking any dose of vitamin C (yes/no) and those taking high doses of vitamin C (≥1000 mg, yes/no). These users were compared to women not frequently taking 'any' or 'high' doses, respectively. The high dose of 1000 mg/d is the recommended safe upper limit; intake at this level and above has been linked to adverse effects, particularly gastrointestinal disturbance[26]. This level is >15 times of the recommended daily allowance (EU RDA = 60 mg/d[27]) normally found in multivitamins. Frequent intake of supplements containing vitamin C in the present study was defined as taking on at least three out of the four diary days. This was compared to frequencies given in the follow-up questionnaire, completed concurrently with the diary. Respondents were asked to indicate which supplements and how often they were taken: more than once a day; daily; weekly; monthly; or less than once a month. The supplements listed included vitamin C, antioxidants, and multivitamins. Sociodemographic and health-related lifestyle variables that were significantly associated with either any dose or high intake were all included in a logistic regression model for mutual adjustment.

Social class and marital status variables were derived from answers to the questionnaire used at recruitment since this information was not provided at follow-up. The combined FFQ and health and lifestyle questionnaire used at recruitment was developed from the one used in the Oxford arm of the European Prospective Investigation into Cancer and Nutrition study[28], which was validated on a subsample of 303 cohort participants[29]. All other variables were taken from responses to the follow-up questionnaire: BMI (kg/m^2); smoking status; level of physical activity; parity; drinking alcohol less than once a week; red meat servings; total fruit and vegetable servings; and frequency of visits to doctors and alternative practitioners. Vigorous activity was defined as activity causing shortness of breath, rapid heart rate and sweating. Attendance at routine health checks was not significantly associated with vitamin C intake, and therefore was excluded from the models.

These variables, excluding visits to doctors and alternative practitioners, were used in logistic regression analyses to adjust the odds of women with a family or personal history of cancers and other health problems taking any or high doses (≥1000 mg) of vitamin C. Personal and family histories of breast cancer and total cancers were the principal analyses. For these and personal histories of the other cancers, additional analyses were performed at doses ≥250, ≥500 and ≥2000 mg. Given that vitamin C supplements are more likely to be taken in winter because well-publicised research had linked it to reduced duration of the seasonal common cold[30], sensitivity analyses were performed to assess the robustness of results to weighting the analyses by the inverse of the probability of being sampled in each season.

All information related to family or personal history of cancers and other illnesses was reported by the participants at follow-up. They were asked whether family members (blood relatives only) ever had medical conditions listed (see Table 4 for types provided) or ever had the following cancers: breast, skin, lung, colon and rectum, ovary, stomach, cervix, ovary, pancreas or prostate. The cancer history of first- and second-degree relatives

was used to identify women potentially at raised or high risk of hereditary breast cancer. It was unknown whether affected relatives were on the same side of the family; therefore, this could only be approximate to the guidelines provided by the UK National Institute for Health and Clinical Excellence[31]. Participants were also asked to report their own history of disease, including whether they had previously been told they had a diagnosis of one of the cancers listed above.

Results

In all, 34% (*n* 4242) of women frequently took supplements containing any dose of vitamin C, on at least three of the four diary days, and 5% (*n* 579) frequently took high doses of ≥1000 mg; 27% (*n* 1165) of those frequently taking any dose and 52% (*n* 299) taking high doses of vitamin C took four or more types of supplements. Furthermore, 82% of users taking any dose and 86% of the high-dose users took some type of supplement at recruitment, on average 4 years earlier.

Substantial agreement ($\kappa = 0{\cdot}70$, 95% CI 0·68, 0·72) was found between answers relating to daily intake of vitamin C, antioxidants or multivitamins in the questionnaire and 3 or 4 d of recorded intake of supplements containing any vitamin C dose in the 4 d diary. In addition, diary recording of doses ≥90 mg taken at this frequency showed substantial agreement ($\kappa = 0{\cdot}72$, 95% CI 0·70, 0·74) with questionnaire responses to daily vitamin C supplementation.

After mutual adjustment, significant lifestyle predictors of frequently taking supplements containing either high dose or any dose of vitamin C were eating more than five servings of fruit and vegetables per day; eating fewer servings of red meat; and visiting an alternative practitioner more often than women not frequently taking these supplements (Table 1). The odds of visiting an alternative practitioner four or more times in the past 12 months were substantially greater for high-dose takers compared to any dose takers (OR = 2·84, 95% CI 2·20, 3·66 *v.* OR = 1·75, 95% CI 1·51, 2·03). In addition, the odds of taking supplements containing any dose of vitamin C were significantly higher in women who exercised vigorously >3 times/week (OR = 1·52, 95% CI 1·23, 1·8); or were aged ≥45 years; of intermediate social class, divorced, childless, frequent visitors to their general practitioner or leaner. Significant predictors of frequent intake of high dose were being an ex-smoker when compared with never smokers (OR = 1·25, 95% CI 1·02, 1·53), drinking alcohol less than once a week (OR = 1·37, 95% CI 1·12, 1·67) and being of high socio-economic status compared to low status (OR = 1·45, 95% CI 1·06, 2·00).

Table 2 shows that, after adjustment, frequent intake of high-dose vitamin C remained significantly associated with a personal history of any cancer (OR = 1·33, 95% CI 1·00, 1·76) and any hormone-related cancer (OR = 1·68, 95% CI 1·16, 2·43), specifically breast cancer (OR = 1·70, 95% CI 1·14, 2·55). In addition, frequent high-dose intake was significantly greater for women with a family history of breast cancer (OR = 1·26, 95% CI 1·01, 1·58) and appeared more likely in women with a family history of any cancer (OR = 1·16, 95% CI 0·95, 1·41), any hormone-related cancer (OR = 1·19, 95% CI 0·98, 1·46) and pancreatic cancer (OR = 1·44, 95% CI 0·94, 2·21). The intake of any dose of vitamin C was significantly associated with a family history of cancer of the uterus (OR = 1·38, 95% CI 1·10, 1·74). These results were very similar when the analysis was weighted to take into account differential sampling in each season. For instance, the seasonally weighted odds of being a high-dose user with a personal history of breast cancer was 1·61 (95% CI 1·07, 2·41), or was 1·29 (95% CI 1·03, 1·62) with a family history of breast cancer or 1·53 (95% CI 0·99, 2·36) with a family history of pancreatic cancer. However, the result for a personal history of total cancers was not significant (OR = 1·30, 95% CI 0·97, 1·73) after seasonal weighting.

It may be observed in Table 3 that the odds of vitamin C use increased with increasing dose >500 mg for women who had any family member with a history of breast cancer or who had a personal history of breast cancer. For the latter, OR were 1·09 (95% CI 0·78, 1·52) at ≥500 mg, 1·70 (95% CI 1·14, 2·55) at ≥1000 mg and 2·36 (95% CI 1·00, 5·56) at ≥2000 mg. A similar pattern occurs for those with a personal history of cancer of the uterus or cervix, and was also seen in the total analyses of any cancer or any hormone-related cancer. The small numbers of women in some of the categories, however, may have produced spurious results. Although the odds of having a mother or sister with breast cancer or potentially being at raised risk of this cancer increased at higher intakes, these were not statistically significant.

It may be observed in Table 4 that high-dose takers also had greater odds of having a personal history of cardiovascular and intestinal disorders after adjustment (OR = 1·27, 95% CI 1·02, 1·59; and OR = 1·25, 95% CI 1·03, 1·51, respectively). Specifically, they had double the odds of a history of angina (OR = 2·05, 95% CI 1·21, 3·45) and an increased risk of reporting haemorrhoids (OR = 1·26, 95% CI 1·01, 1·56), irritable bowel syndrome (IBS; OR = 1·27, 95% CI 0·98, 1·64) and anal fissures (OR = 1·41, 95% CI 0·95, 2·09). Generally, vitamin C supplementation was not significantly associated with a family history of morbidities in Table 4; however, a high intake was significantly associated with a family history of high blood pressure (OR = 1·30, 95% CI 1·07, 1·57), and any vitamin C intake was significantly associated with a family history of high cholesterol (OR = 1·16, 95% CI 1·01, 1·33). The use of supplements containing any dose of vitamin C was significantly associated with both a family and personal history of arthritis. Conversely, women with diabetes mellitus were less likely to take them.

Table 1 Characteristics associated with the intake of supplements containing any dose of vitamin C and the intake of supplements containing high doses of vitamin C (≥1000 mg)

	Any dose			≥1000 mg		
Characteristics	OR*	95 % CI	*P* value	OR*	95 % CI	*P* value
Age (years)†						
<45	1·00	Ref.	0·07	1·00	Ref.	0·3
45–54	1·20	1·03, 1·41		1·11	0·81, 1·54	
55–64	1·26	1·07, 1·48		0·85	0·60, 1·20	
≥65	1·23	1·03, 1·47		0·91	0·62, 1·34	
Social class‡						
High	1·00	Ref.	0·1	1·00	Ref.	0·04
Intermediate	1·10	1·01, 1·21		0·96	0·78, 1·17	
Low	1·07	0·94, 1·22		0·69	0·50, 0·94	
Marital status‡						
Married or living together	1·00	Ref.	0·4	1·00	Ref.	0·9
Divorced/separated	1·31	1·14, 1·51		1·25	0·94, 1·66	
Widowed	0·95	0·78, 1·16		1·14	0·72, 1·80	
Single	0·86	0·72, 1·03		0·88	0·61, 1·28	
Had children						
Yes	1·00	Ref.	0·001	1·00	Ref.	0·09
No	1·24	1·11, 1·39		1·23	0·97, 1·56	
BMI (kg/m^2)†						
Underweight (<18·00)	1·03	0·72, 1·46		1·07	0·53, 2·15	
Normal (18·00–24·99)	1·00	Ref.	0·08	1·00	Ref.	0·6
Overweight (25·00–29·99)	0·90	0·82, 0·99		0·87	0·69, 1·09	
Obese (≥30·00)	0·93	0·80, 1·07		1·11	0·81, 1·54	
Smoking status‡						
Never smoked	1·00	Ref.	0·4	1·00	Ref.	0·02
Ex-smoker	1·07	0·98, 1·17		1·25	1·02, 1·53	
Current smoker	0·91	0·75, 1·00		1·19	0·79, 1·81	
Drinks alcohol more than once a week						
Yes	1·00	Ref.	0·1	1·00	Ref.	0·001
No	1·07	0·98, 1·17		1·37	1·12, 1·67	
Physical activity‡						
No weekly physical activity	1·00	Ref.	<0·001	1·00	Ref.	0·008
Light moderate (most weeks)	1·16	0·95, 1·41		0·94	0·60, 1·48	
Vigorous (1–2 times/week)	1·18	0·96, 1·46		0·98	0·61, 1·57	
Vigorous (≥3 times/week)	1·52	1·23, 1·89		1·36	0·85, 2·19	
Servings of red meat eaten/week‡						
None	1·00	Ref.	<0·001	1·00	Ref.	<0·001
1–3	0·79	0·72, 0·87		0·68	0·55, 0·85	
≥4	0·61	0·54, 0·68		0·48	0·35, 0·65	
Servings of fruit and vegetables eaten/d‡						
≤2	1·00	Ref.	<0·001	1·00	Ref.	0·01
3–5	1·21	1·08, 1·37		1·11	0·84, 1·48	
>5	1·45	1·26, 1·67		1·40	1·02, 1·92	
Number of visits to doctors in past 12 months‡						
None	1·00	Ref.	<0·001	1·00	Ref.	0·9
1–4	1·27	1·12, 1·42		0·98	0·76, 1·25	
>4	1·45	1·26, 1·67		0·98	0·72, 1·33	
Number of visits to alternative practitioners in past 12 months‡						
None	1·00	Ref.	<0·001	1·00	Ref.	<0·001
1–4	1·41	1·23, 1·61		1·77	1·35, 2·31	
>4	1·75	1·51, 2·03		2·84	2·20, 3·66	
Number of participants in the models	10 161			10 161		

Ref., reference category.
*Mutually adjusted for the other variables listed above.
†*P* for trend over the continuous variables.
‡*P* for trend over categories.

Discussion

The frequent intake of supplements containing any dose or high doses of vitamin C in the UKWCS was associated with healthier lifestyle behaviours, and therefore supports the inverse supplement hypothesis, as seen in the analyses of any supplement intake in the UK or elsewhere[4,7–14]. Women taking either high (≥1000 mg/d) or any dose of vitamin C were more likely to consume over five servings of fruit and vegetables, the main dietary source of vitamin C[17]. This is consistent with evidence from the studies of any supplement intake[6,7,12] and US studies on the intake of vitamin C supplements[9,12], and suggests that many high-dose vitamin C takers are less likely to need them. Furthermore, in line with US findings, UKWCS vitamin C takers were likely to eat less meat[10].

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Table 2 OR of taking supplements containing vitamin C: any dose or ≥1000 mg for UKWCS women who self-reported a personal or a family history of cancer

		Any dose (*n* 4242; 34 %)				≥1000 mg (*n* 579; 5 %)			
		Unadjusted		Adjusted*		Unadjusted		Adjusted*	
Type of cancer	*n*†	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Personal history									
Any cancer	1268	1·14	1·01, 1·29	1·12	0·97, 1·28	1·31	1·02, 1·68	1·33	1·00, 1·76
Any hormone	642	1·11	0·94, 1·31	1·08	0·89, 1·31	1·50	1·09, 2·08	1·68	1·16, 2·43
Breast	523	1·13	0·94, 1·36	1·10	0·89, 1·35	1·53	1·08, 2·18	1·70	1·14, 2·55
Uterus	75	0·85	0·52, 1·39	0·77	0·44, 1·34	1·78	0·77, 4·12	1·97	0·77, 5·02
Ovarian	60	1·29	0·77, 2·17	1·28	0·71, 2·33	1·35	0·60, 3·07	0·84	0·20, 3·51
Any non-hormone cancer	584	1·16	0·98, 1·40	1·11	0·91, 1·34	1·16	0·80, 1·70	1·05	0·68, 1·60
Skin	324	1·14	0·91, 1·43	1·04	0·81, 1·34	0·85	0·48, 1·49	0·71	0·36, 1·39
Cervix	190	1·26	0·94, 1·69	1·20	0·86, 1·66	2·03	1·22, 3·36	1·70	0·94, 3·05
Colon/rectum	63	1·19	0·71, 1·98	1·30	0·73, 2·30	1·07	0·34, 3·44	0·98	0·24, 4·10
Family history									
Any cancer	7259	1·08	1·00, 1·16	1·04	0·96, 1·13	1·15	0·97, 1·36	1·16	0·95, 1·41
Any hormone cancer	3629	1·09	1·01, 1·18	1·09	0·99, 1·19	1·16	0·97, 1·38	1·19	0·98, 1·46
Breast	2370	1·06	0·97, 1·17	1·04	0·94, 1·16	1·23	1·00, 1·51	1·26	1·01, 1·58
Prostate	958	1·09	0·95, 1·25	1·13	0·97, 1·32	1·04	0·76, 1·41	1·09	0·77, 1·51
Ovarian	423	1·10	0·90, 1·35	1·12	0·90, 1·41	1·07	0·69, 1·70	1·09	0·66, 1·79
Uterus	380	1·41	1·14, 1·73	1·38	1·10, 1·74	1·08	0·68, 1·73	1·11	0·66, 1·87
Any non-hormone cancer	5227	1·07	0·99, 1·16	1·03	0·95, 1·12	1·03	0·87, 1·22	1·04	0·86, 1·25
Lung	2066	1·06	0·96, 1·17	1·00	0·89, 1·11	1·07	0·86, 1·33	1·00	0·78, 1·29
Colon/rectum	1608	0·96	0·86, 1·08	0·98	0·86, 1·11	0·97	0·76, 1·25	1·08	0·82, 1·43
Stomach	1300	1·02	0·90, 1·15	1·01	0·88, 1·16	0·91	0·69, 1·21	0·97	0·71, 1·33
Skin	957	1·01	0·88, 1·16	0·97	0·83, 1·13	0·88	0·64, 1·23	0·86	0·60, 1·24
Pancreas	455	1·13	0·93, 1·37	1·11	0·90, 1·38	1·41	0·96, 2·08	1·44	0·94, 2·21
Cervix	311	1·03	0·81, 1·31	1·04	0·79, 1·36	0·68	0·36, 1·28	0·74	0·38, 1·46

*Adjusted for BMI, age, social class, marital status, children, smoking status, level of physical activity, low alcohol consumption, red meat servings, total fruit and vegetable servings.
†Total numbers with history of cancer.

They also exercised vigorously more often, supporting previous research linking activity to supplement intake[6–8,11–14]. Distinguishing characteristics of high-dose vitamin C takers in the UKWCS were being an ex-smoker, drinking alcohol less than once a week and being of high socio-economic status. These characteristics were not significant predictors of using supplements containing any dose of vitamin C in the UKWCS; however, they have been positively associated with taking any type of supplement in other studies[5,8]. In addition, high-dose vitamin C takers appeared to rely more on alternative practitioners rather than family or private doctors. Healthy behaviours associated with the intake of vitamin C supplements are likely to reduce health risks; therefore, these behaviours identified should be considered for adjustment in longitudinal studies of risks[12].

Despite controversy surrounding evidence of benefits of high-dose vitamin C supplementation for prolonged cancer survival[32–34], our results showed prior to seasonal weighting that women with any type of cancer were more likely to be high-dose vitamin C supplement takers than women with no history of cancer. Since antioxidants can potentially reduce the effectiveness of anti-cancer drugs[35,36], patients should be encouraged to discuss their supplement use with their doctors in order to avoid contraindications. For some cancer patients, supplement use may be a coping behaviour and a way of taking control[37,38]. Similar health-related behaviours may also occur in women with concerns about risk of developing cancer: for instance, women who attended mammography have also been positively associated with the intake of supplements in the USA[12]. Similarly, women attending UK breast screening clinics had similar characteristics to supplement takers in the UKWCS and wanted diet and exercise advice to be provided at these clinics[39]. Lower doses and any dose of vitamin C, however, were not significantly associated with total cancer in the UKWCS; this has also been observed in some US studies[22,40].

To the best of our knowledge, this is the first UK study to analyse associations between the use of vitamin C supplements and specific prevalent cancers, and therefore the first to report significant associations of frequent intake of high-dose vitamin C (≥1000 mg/d) in UK women with a personal or family history of breast cancer. This supports findings that US women physicians with breast cancer were more likely to take vitamin C[10]. Furthermore, our results show that the odds of having a history of cancer increased at higher doses (≥2000 mg). However, while US research found that women at a high risk of breast cancer and with inconclusive genetic test results were significantly more likely to take any supplements, the increased odds of high-dose vitamin C

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Table 3 OR of taking supplements containing vitamin C for a range of doses for the UK Women's Cohort Study women who self-reported a personal history of cancer or a family history of breast cancer

	Frequent intake of vitamin C doses											
	≥250 mg (*n* 1448; 12 %)			≥500 mg (*n* 1195; 10 %)			≥1000 mg (*n* 579; 5 %)			≥2000 mg (*n* 92; 1 %)		
	n†	OR*	95 % CI	*n*†	OR*	95 % CI	*n*†	OR*	95 % CI	*n*†	OR*	95 % CI
Personal history												
Any cancer	159	1·06	0·87, 1·30	131	1·03	0·83, 1·29	74	1·33	1·00, 1·76	19	2·86	1·64, 4·98
Any hormone cancer	81	1·04	0·79, 1·39	69	1·08	0·80, 1·46	43	1·68	1·16, 2·43	12	3·50	1·75, 7·01
Breast cancer	68	1·10	0·81, 1·49	56	1·09	0·78, 1·52	36	1·70	1·14, 2·55	8	2·36	1·00, 5·56
Uterus	8	0·99	0·45, 2·22	8	1·25	0·56, 2·78	6	1·97	0·77, 5·02	3	8·64	2·52, 29·6
Ovarian	7	0·50	0·15, 1·62	7	0·64	0·20, 2·06	3	0·84	0·20, 3·51	1	2·75	0·37, 20·8
Any non-hormone cancer	69	0·98	0·73, 1·30	56	0·97	0·71, 1·33	31	1·05	0·68, 1·60	8	2·52	1·19, 5·32
Skin	34	0·79	0·53, 1·20	26	0·74	0·47, 1·19	13	0·71	0·36, 1·39	2	1·08	0·26, 4·49
Cervix	32	1·43	0·93, 2·21	29	1·60	1·03, 2·52	17	1·70	0·94, 3·05	4	3·14	1·10, 8·94
Colon/rectum	5	0·69	0·24, 1·94	3	0·41	0·10, 1·72	3	0·98	0·24, 4·10	2	7·20	1·62, 32·1
Family history of breast cancer												
Any family member	299	1·15	0·99, 1·34	244	1·10	0·93, 1·30	129	1·26	1·01, 1·58	27	1·69	1·01, 2·83
Mother or sister	163	1·13	0·93, 1·37	129	1·04	0·84, 1·29	67	1·16	0·87, 1·55	15	1·55	0·81, 2·96
Respondent at raised risk	32	1·11	0·73, 1·68	25	1·04	0·66, 1·65	15	1·31	0·73, 2·32	4	2·03	0·62, 6·56
Respondent at high risk‡	9	0·67	0·30, 1·47	8	0·71	0·31, 1·65	4	0·69	0·22, 2·23			

*Adjusted for BMI, age, social class, marital status, children, smoking status, level of physical activity, low alcohol consumption, red meat servings, total fruit and vegetable servings. Comparison group = all respondents not taking stated dose.
†Total numbers with a history of cancer listed taking doses specified.
‡Insufficient numbers at higher doses.

Table 4 OR of taking supplements containing vitamin C: any dose or ≥1000 mg for the UK Women's Cohort Study women who self-reported a family history or personal history of other illnesses

		Any dose				≥1000 mg (yes/no)			
		Unadjusted		Adjusted*		Unadjusted		Adjusted*	
Type of illness	*n*	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Personal history									
CV-related disorders	3217	0·90	0·83, 0·98	0·98	0·89, 1·09	1·00	0·83, 1·21	1·27	1·02, 1·59
Heart attack	176	0·83	0·60, 1·15	0·90	0·62, 1·30	1·22	0·64, 2·33	1·63	0·81, 3·30
Angina	293	0·90	0·70, 1·15	1·07	0·81, 1·41	1·42	0·88, 2·29	2·05	1·21, 3·45
Stroke	172	1·15	0·84, 1·57	1·13	0·79, 1·60	1·13	0·58, 2·23	1·50	0·72, 3·11
High blood pressure	2302	0·88	0·80, 0·97	0·97	0·87, 1·09	0·96	0·77, 1·19	1·20	0·93, 1·54
High cholesterol	1246	0·99	0·88, 1·12	1·07	0·92, 1·23	0·98	0·74, 1·29	1·19	0·86, 1·64
Diabetes	265	0·64	0·48, 0·84	0·71	0·51, 0·98	0·47	0·21, 1·06	0·62	0·25, 1·53
Gallstones	748	0·97	0·83, 1·13	1·00	0·83, 1·19	0·96	0·68, 1·37	1·04	0·69, 1·57
Intestine disorders	4716	1·21	1·12, 1·30	1·23	1·13, 1·34	1·22	1·03, 1·45	1·25	1·03, 1·51
Polyps	179	0·88	0·64, 1·21	0·93	0·65, 1·33	0·83	0·39, 1·80	1·02	0·44, 2·34
Stomach ulcer	941	1·17	1·02, 1·34	1·20	1·02, 1·39	1·02	0·75, 1·39	1·14	0·82, 1·61
IBS	1650	1·30	1·17, 1·44	1·31	1·16, 1·47	1·27	1·01, 1·60	1·27	0·98, 1·64
Haemorrhoids	2716	1·08	0·99, 1·18	1·07	0·97, 1·19	1·23	1·01, 1·49	1·26	1·01, 1·56
Ulcerative colitis	140	0·98	0·69, 1·40	1·05	0·69, 1·58	1·07	0·50, 2·30	1·07	0·43, 2·65
Diverticular	453	0·88	0·72, 1·08	0·97	0·77, 1·22	0·69	0·41, 1·16	0·65	0·33, 1·28
Anal fissure	561	1·20	1·01, 1·43	1·17	0·96, 1·43	1·29	0·89, 1·85	1·41	0·95, 2·09
Arthritis	3391	1·20	1·10, 1·30	1·32	1·19, 1·45	0·97	0·80, 1·17	1·17	0·93, 1·47
Family history									
CV-related disorders	9765	1·03	0·94, 1·12	1·01	0·91, 1·12	1·20	0·97, 1·48	1·24	0·96, 1·59
Heart attack	5558	1·05	0·97, 1·13	1·06	0·97, 1·15	1·12	0·95, 1·32	1·11	0·92, 1·34
Angina	2982	0·97	0·89, 1·06	0·95	0·86, 1·05	1·20	0·99, 1·45	1·12	0·91, 1·38
Stroke	3799	1·04	0·96, 1·13	1·00	0·91, 1·09	0·93	0·77, 1·12	0·88	0·72, 1·09
High blood pressure	4358	1·05	0·97, 1·13	1·03	0·94, 1·12	1·29	1·09, 1·53	1·30	1·07, 1·57
High cholesterol	1185	1·13	0·99, 1·28	1·16	1·01, 1·33	1·21	0·93, 1·58	1·21	0·90, 1·61
Diabetes	2320	1·01	0·92, 1·11	1·03	0·92, 1·14	1·07	0·87, 1·33	1·13	0·90, 1·43
Intestine disorders	3102	1·07	0·98, 1·17	1·07	0·97, 1·18	0·99	0·81, 1·20	1·00	0·81, 1·24
Polyps	295	1·12	0·88, 1·42	1·09	0·83, 1·42	0·64	0·33, 1·25	0·50	0·22, 1·14
Stomach ulcer	1821	1·05	0·94, 1·16	1·03	0·92, 1·16	0·90	0·71, 1·15	0·90	0·69, 1·19
IBS	1007	1·06	0·93, 1·22	1·10	0·94, 1·28	1·23	0·93, 1·63	1·34	0·99, 1·82
Ulcerative colitis	324	0·99	0·79, 1·26	0·99	0·76, 1·28	1·07	0·64, 1·78	1·27	0·75, 2·18
Anal fissure	221	1·31	1·00, 1·72	1·30	0·96, 1·75	0·67	0·31, 1·42	0·53	0·21, 1·29
Arthritis	5165	1·20	1·12, 1·30	1·19	1·10, 1·30	1·12	0·95, 1·33	1·09	0·90, 1·31

CV, cardiovascular; IBS, irritable bowel syndrome.
*Adjusted for BMI, age, social class, marital status, no children, smoking status, level of physical activity, low alcohol consumption, red meat servings, total fruit and vegetable servings.

intake in the UKWCS for women with increased risk of hereditary breast cancer or those having mothers or sisters with breast cancer were not significant[41]. Our results may be due to low numbers and lack of power. In general, a history of non-hormone-related cancer did not appear to be associated with the intake of vitamin C supplements in the UKWCS. Nevertheless, associations with a personal history of cervical cancer remained significant at some doses after adjustments, including adjustment of socio-economic status, which is known to be linked with this cancer[42].

In relation to the prevention of cancer, CVD and other chronic diseases, the 5-A-Day fruit and vegetable initiative based on the WHO recommendations could have influenced antioxidant supplement sales at the time of the UKWCS follow-up[43]. Proactive marketing by supplement companies would have also increased sales. The 1997 WCRF report, nevertheless, stated that supplements were probably unnecessary and unhelpful in reducing the risk of cancer[44]. While the recent 2007 WCRF report found no probable or convincing evidence that vitamin C supplementation affects the risk of cancer, there was evidence of an increased or decreased risk with some other supplement types, although this was usually from studies of high-risk groups[1]. In summary, the 2007 report states that it is unwise to recommend widespread supplement use for the prevention of cancer since the effects cannot be confidently predicted in the general population[1]. Indeed, high doses of some supplements, including vitamin C, may promote cancer[35], although doses >400 mg of this water-soluble vitamin are likely to be excreted in healthy women[45]. Its antioxidant properties may reduce DNA damage by reactive oxygen species (ROS) during the initial stage of cancer, particularly in individuals with high levels of ROS[35]. This antioxidant property, however, may decrease beneficial apoptosis, the ROS-induced programmed death of damaged cells[46], and thereby lead to the progression of cancer, particularly in individuals with

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low levels of ROS[35]. Vitamin C may also act as a pro-oxidant creating highly reactive and damaging hydroxyl radicals via the Fenton reaction in the presence of iron[47]. However, this hypothesis is controversial since free iron is normally unavailable *in vivo*[47]. Apart from a family history of breast cancer and a moderate but non-significant association with a family history of pancreatic cancer, our results indicate that UK women were probably not taking high vitamin C supplements as a preventive measure due to a family history of cancer in general. Since cancer of the pancreas has a poor prognosis, women with this family history may have been more motivated to take high doses of vitamin C supplements.

In general, UKWCS respondents did not appear to take vitamin C for the prevention of other morbidities observed in their families. Only women with a family history of high blood pressure were significantly more likely to use a high dose of vitamin C, and those with a family history of high cholesterol or arthritis were significantly more likely to take any dose of vitamin C. In fact, a reduction in the risk of inflammatory polyarthritis (rheumatoid arthritis) has been linked to antioxidant intake[48]. Despite inconsistent evidence relating to associations between vitamin C supplementation and reduced CHD and hypertension[18–20,49], women in the UKWCS, who had personally experienced cardiovascular-related diseases, specifically angina, were more likely to be high-dose users. Furthermore, US female physicians with hypertension were found to use vitamin C frequently[10]. However, this is not always the case since another US study found that risk factors for CVD were inversely associated with frequent intake of vitamin C (≥150 mg/d)[22]. Similarly, women with diabetes in our study were less likely to take any dose of vitamin C; it is unknown whether the burden of diabetic medication deters supplement taking or whether low levels of health literacy or health consciousness confound the negative association.

It is unknown why vitamin C supplements were used by women in the UKWCS. Given that only a relative small proportion of the UK population is advised by the medical profession to take a supplement for health reasons[5], some health-conscious UK women with chronic conditions may be self-treating with vitamin C. Alternatively, those with disorders may use supplements under the belief that supplements can make them feel better generally or increase immune function[50]. In addition, due to the cross-sectional nature of the study the direction of cause and effect cannot be determined; it is unknown whether vitamin C has been taken to prevent or manage symptoms of disorders or whether vitamin C has caused them. For instance, the associations observed with IBS could have been due to abdominal pain and diarrhoea caused by taking large doses of vitamin C[51]. However, the significant associations with IBS occurred at any dose of vitamin C, rather than at high dose specifically; therefore, a plausible explanation is that very health-conscious women who take supplements may be prone to anxiety, which might cause IBS[52]. This pattern of associations may reflect supplementing with multivitamins or antioxidant combinations containing vitamin C; the pattern was also seen with both a personal and family history of arthritis in the present study.

Lack of information to determine whether medical conditions developed before or after frequent intake of vitamin C supplements started is a limitation of the present study. Although data from the cancer registry were available for the cohort, we suggest that it is women's self-reported perceived health, whether accurate or not, that influences their supplement intake behaviour. Self-reporting of supplement descriptions for only 4 d by diary was a limitation of the study. While 4 d diaries are capable of capturing daily, and near daily intake, in reality some 3–4 d diary recordings may represent spasmodic rather than frequent intake. Nevertheless, our results show that substantial agreement was found between these frequent diary recordings and daily use recorded concurrently by the questionnaire. Although the number of years of supplementation was not collected in either the diary or the questionnaire, and no further follow-up was conducted, the majority of vitamin C users (82 %) were taking a supplement of some type on average 4 years earlier at recruitment. An additional problem was the wide variety of formulations of supplements used, which made coding difficult. While high-dose vitamin C supplements were unlikely to contain other micronutrients[14], our results show that, consistent with other research[5], women taking high doses were highly likely to use other supplements. Therefore, vitamin C use may be a marker for the intake of other supplements.

Our study capitalises on the large sample size of the UKWCS, substantial numbers of women frequently taking vitamin C (34 %) and as well as the wide variety of characteristics and self-reported illnesses recorded. However, the small numbers of women in some of the categories, particularly those shown in Table 3, and especially those taking ≥2000 mg/d, may have produced spurious results. Another limitation of the present study is that the UKWCS participants were more health conscious than the general population and therefore not representative of the whole UK population. Differences in characteristics between frequent users and non-frequent users in the UKWCS may not be as pronounced as that found in the general population.

Our research may help to identify high-dose users, such as ex-smokers, low alcohol drinkers and women with a history of breast cancer or other illnesses, who could be made aware of the inconsistencies in evidence relating to suggested benefits and about warnings relating to high-strength supplements[53]. Furthermore, patients should be encouraged to discuss their supplement use with their doctors to avoid contraindications[36,46]. Finally, additional research is needed to establish the effects of both supplement and dietary vitamin C intake on cancer initiation and development, as well as other illnesses.

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