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Vitamin C supplement use and a history of cancer (short title)

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High dose vitamin C supplement use is associated with a history of cancer and other illnesses in the UK Women's Cohort Study

Abstract (Words 250)

Objective: To determine whether regular vitamin C supplement use is associated with healthier behaviours, and a history of cancer and other illness in UK women.

Design: This cross-sectional analysis examines the odds of taking supplements containing vitamin C as recorded in 4-day food diaries, based on lifestyle characteristics and morbidity history self-reported by questionnaire.

Subjects: 12,453 middle-aged women from the UK Women's Cohort Study (UKWCS).

Results: Women regularly taking supplements containing vitamin C, compared to those than did not, had healthier behaviours, including higher consumption of fruit and vegetables. Regular high dose vitamin C takers (>=1000mg) had a higher socioeconomic 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 with a self-reported personal or family history of cancer had increased odds of being regular high dose users ((OR=1.33 (95% CI: 1.00, 1.76) and OR=1.16 (95% CI: 0.95, 1.41) respectively after adjusting for socio-demographic and health behaviours). Specifically, high dose vitamin C taking was significantly associated with personal (OR=1.70 (95% CI: 1.14, 2.55)) or family (OR=1.26 (95% CI: 1.01, 1.58)) history of breast cancer. 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.

Conclusion: High dose vitamin C taking by UK women was associated with healthier behaviours and a history of breast cancer, total cancer and other illnesses. Patient guidelines for their use may be needed.

Introduction

Despite lack of evidence of benefits, vitamin supplement-taking reported by UK women increased from 17% in 1986/1987 to 41% reported in 2008/9[1,2]. Users are most likely to be women above 55yrs and of higher socioeconomic status[3]. 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 body mass index (BMI) and eat diets which met recommended dietary intakes. Therefore they were less likely to need supplements than non-users[4]. Further support for this 'inverse supplement hypothesis' has been found in the UK[2,5,6], and elsewhere[7-12]. Moreover, those classifying themselves as high strength supplement users in a recent UK survey were particularly health conscious[3].

Vitamin C is one of the most commonly used supplements in the UK[3,13]. However, suggestions that it is able to reduce the incidence of colds, have been unsubstantiated in randomised controlled trials[14,15]. Furthermore, despite clear evidence of an association between plasma vitamin C levels and reduced mortality from all-causes, from cardiovascular disease, and from ischemic heart disease[16], there is limited evidence to suggest that vitamin C supplement-taking is associated with reduced risk of chronic diseases[17].

Although general supplement use is particularly widespread in cancer survivors in the US, with breast cancer survivors showing the highest use[18], no overall association between vitamin C supplement-taking (>=150mg) and prevalent cancer was found in the US Vitamins and Lifestyle (VITAL) cross-sectional study[19]. Furthermore those with pre-existing diabetes, hypertension, cardiovascular disease (CVD) were less likely to use them[19]. 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[8].

UK health-conscious cancer survivors were also more likely to take any supplement than cancer free women[13]; however, other pre-existing chronic diseases have been inversely associated with taking vitamins, minerals or antioxidants in a UK study combining men and women[5]. To the best of our knowledge no study has examined the relationship between vitamin C supplement-taking in UK women and lifestyle factors or personal or family history of morbidities. Our study capitalises on the large sample size of the UKWCS, substantial numbers of women regularly

taking vitamin C (34%) and the wide variety of characteristics and self-reported illnesses recorded. The main aims of the study were to determine whether vitamin C supplement-taking in the UKWCS was associated with healthier behaviours, and whether women with a history of cancer, in particular breast cancer, were more likely to use them.

Methods

UKWCS recruitment data was gathered between1995-1998 from 35,367 women who completed a 217-item Food frequency questionnaire (FFQ)[20-22]. This national cohort of mainly caucasian, well-educated, middle-class, middle-aged, married women was designed to compare disease incidence in vegetarians, fish-eaters and meat-eaters[20]. At recruitment 62% of participants took some type of dietary supplement.

Two to five years after recruitment, all the initial participants were re-contacted and 12,453 (35%) completed a follow-up questionnaire and a 4-day 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 composition obtained from product labels provided by participants, suppliers' websites or provided directly from manufacturers. The average daily vitamin C intake contained in all supplement types was calculated for the total number of diary days vitamin C was taken.

Using Stata version 10, unvariable logistic regression was applied to determine which participant characteristics predicted regular supplement-taking in two different classifications of users: those taking any dose of vitamin C (y/n); and those taking high doses of vitamin C (>=1000mg, y/n). These were compared to women not regularly taking 'any' or 'high' doses respectively. This high dose of 1000mg/day is the recommended safe upper limit; intakes at this level and above have been linked to adverse effects, particularly gastrointestinal disturbance[23]. This level is more than 15 times the recommended daily allowance (EU RDA = 60mg/day[24]) normally found in multivitamins. Regular taking in this study was defined as taking on at least three out of the four diary days. Diary recording of doses >=90mg taken at this frequency showed substantial agreement with responses to daily vitamin C use reported on a separate questionnaire. Socio-demographic 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. Table 1 shows the categorisation of continuous and discrete variables and also displays the significance for trend values.

Social class and marital status variables used information gathered by questionnaire at recruitment. 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 portions; total fruit and vegetable portions; 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 taking, 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 (>=1000mg) of vitamin C. Personal and family histories of breast cancer and total cancers were the principle analyses. For these and personal histories of the other cancers additional analyses were performed at doses above or equal to 250mg; 500mg; and 2000mg. Since vitamin C supplements are more likely to be taken in winter 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 relating to family or personal history of cancers and other illnesses was reported by the participant at follow-up. They were asked whether or not 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 approximate to the guidelines provided by the UK's Nation Institute for Health and Clinical Excellence (NICE)[25]. 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

Thirty four percent (4242) of women regularly took supplements containing any dose of vitamin C, and 5% (579) regularly took high doses of 1000mg or more. Twenty seven percent (1165) of those regularly taking any dose and 52% (299) taking high doses of vitamin C took 4 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.

After mutual adjustment, significant lifestyle predictors of regularly taking supplements containing either high dose or any dose of vitamin C were eating more than 5 portions of fruit and vegetables per day; eating less portions of red meat; and visiting an alternative practitioner more often than women not regularly taking these supplements (table 1). Odds of visiting an alternative practitioner 4 or more times in the last 12 months were substantially greater for high dose takers compared to any dose takers ((OR=2.84 (95% CI: 2.20, 3.66) vs OR=1.75 (95% CI: 1.51, 2.03)). Additionally, the odds of taking supplements containing any dose of vitamin C were significantly higher in women who were aged 45yrs or more; of intermediate social class; divorced; childless; exercised vigorously more than 3 times a week (OR=1.52 (95% CI: 1.23, 1.8)); regular visitors to their GP; or leaner. Significant predictors of regular high dose taking 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).

Insert table 1 here

Table 2 shows that, after adjustment, regular high dose taking of 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). Additionally, regular high dose taking 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)). Taking 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 almost identical when the analysis was weighted to take into account differential sampling in each season.

Table 3 shows that the odds of taking vitamin C increased with increasing dose above 500mg for women who had any family member with a history of breast cancer or who had a personal history of breast cancer e.g. OR=1.09 (95% CI 0.78, 1.52) at >=500mg, OR=1.70 (95% CI 1.14,

2.55) at >=1000mg and OR=2.36(95% CI 1.00, 5.56) at intakes of 2000mg or above. A similar pattern occurs for those with a personal history of cancer of the uterus or cervix, and was 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 influenced the results. Although the odds of having a mother or sister with breast cancer or potentially being at raised risk of this cancer increased with increasing intake, these were not statistically significant.

Insert table 2 here

Insert table 3 here

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) & OR=1.25 (95% CI: 1.03, 1.51) respectively). Specifically they had double the odds of angina (OR=2.05 (95% CI: 1.21, 3.45) and an increased risk of having haemorrhoids (OR=1.26 (95% CI: 1.01, 1.56), irritable bowel syndrome (OR=1.27 (95% CI: 0.98, 1.64) and anal fissures (OR=1.41 (95% CI: 0.95, 2.09). Generally vitamin C intake was not significantly associated with a family history of morbidities in Table 4, however 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 family and personal history of arthritis. Conversely, women with diabetes mellitus were less likely to take them.

Insert table 4 here

Discussion

The regular 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 analyses of any supplement-taking in the UK or elsewhere[5-12]. Women taking either high (>=1000mg per day) or any dose of vitamin C were more likely to consume greater than 5 portions of fruit and vegetables, the main dietary source of vitamin C. This is consistent with evidence from studies of any supplement-taking[4,5,10], and US studies of vitamin C supplement-taking[7,10], 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[8]. They also exercised vigorously more frequently, supporting previous research linking activity to supplement taking[4-6,9-12]. Distinguishing characteristics of high dose vitamin C takers in the UKWCS which were not significant predictors of any dose taking were being an ex-smoker, drinking alcohol less than once a week and being of high socio-economic status; these characteristics nevertheless have been positively associated with taking any type of supplement in other studies[3,6]. Additionally, high dose vitamin C takers appeared to rely more on alternative practitioners rather than family or private doctors. Health behaviours associated with vitamin C supplement taking are likely to reduce health risks, therefore those behaviours identified should be considered for adjustment in longitudinal studies of risks[10].

Despite controversy surrounding evidence of benefits of high vitamin C supplementation for prolonged cancer survival[26-28], our results show 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[29,30] 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[31,32]. 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 supplement taking in the US[10]. Likewise, 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[33].

To the best of our knowledge this is the first UK study to analyse associations between vitamin C supplement-taking and specific prevalent cancers, and therefore the first to report significant associations of regular high dose vitamin C taking (=>1000mg/day) in 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[8]. Furthermore, our results show the odds of taking a vitamin C supplement increased at higher doses (>2000mg). However, whilst US research found that women at high risk of breast cancer and with inconclusive genetic test results were significantly more likely to take supplements, the increased odds of taking high doses of vitamin C in the UKWCS for women with increased risk of hereditary breast cancer or those having mothers or sisters with breast cancer were not significant[34]. 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 vitamin C supplement-taking 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[35].

In relation to cancer prevention, the 1997 World Cancer Research Fund (WCRF) report, issued several years before the initiation of the UKWCS follow-up, stated that diets high in fruit and vegetables probably protected against cancer of the pancreas, stomach and lung, and that fruit, vegetables and vitamin C possibly protected against cervical cancer[36]. Promotion of these findings could have influenced supplement-taking at the time despite the report stating that supplements were probably unnecessary and unhelpful for reducing cancer risk[36]. The recent WCRF 2007 report clearly states that supplements are not recommended for cancer prevention[37]. Indeed high doses of some supplements, including vitamin C may promote the initiation of cancer[38], additionally the vitamin may exhibit different mechanisms at cancer initiation than at later stages[39]. Apart from 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 preventative measure due to a family history of cancer in general. Since cancer of the pancreas has a poor diagnosis, women with this family history may have been more motivated to take high doses of vitamin C supplements.

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 associations with irritable bowel syndrome (IBS) could have been caused by side effects of taking large doses of vitamin C[40]. However, the significant associations with IBS occurred at any dose of vitamin C, rather than 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.

It is unknown why vitamin C supplements were taken by women in the UKWCS. Given that only 17% of UK supplement users are advised to take supplements by their health practitioner[3], with many others taking advice from friends, family, books and magazines[31,41], some health conscious UK women with chronic conditions may be self-treating with vitamin C. Alternatively, those with disorders may take supplements to feel better in general or to increase immune function rather than to treat a condition itself[42]. Despite inconsistent evidence relating to links between vitamin C supplementation and a reduction in coronary heart disease and hypertension[43-45], US female physicians with hypertension have been found to regularly take vitamin C[8]. Conversely, another US study found cardiovascular disease risk factors were inversely associated with regularly taking vitamin C >=150mg/day. 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 a lack of interest in health confounds the negative association.

Limitations of the study include self-reporting of medical conditions and lack of information to determine whether these developed before or after regular vitamin C supplement-taking started. Supplement descriptions were also self-reported, and for only four days by diary, nevertheless substantial agreement was found between this and daily taking recorded by questionnaire. Although the number of years of taking was not collected, and no further diary follow-up was conducted, the majority of vitamin C users (81%) were taking a supplement of some type on average 4 years earlier at recruitment. Associations with taking any dose vitamin C, for instance with arthritis, were likely to reflect taking of multivitamins or antioxidant combinations which contain vitamin C. Whilst high vitamin C dose supplements were unlikely to contain other ingredients,[12] our results show that consistent with other research,[3] women taking high doses

were highly likely to take other supplements. Therefore vitamin C use may be a marker for intake of other supplements. An additional problem was the wide variety of formulations of supplements taken which made coding difficult.

Another limitation of our study is that UKWCS participants were more health conscious than the general population and therefore not representative of the whole UK population. Differences in characteristics between regular takers and non-regular takers 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 educated about inconsistencies in evidence relating to suggested benefits, and about warnings relating to high strength supplements[46]. Furthermore, patients should be encouraged to discuss their supplement-taking with their doctors to avoid contraindications[29,30]. 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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Table 1 Characteristics associated with taking supplements containing any dose of vitamin C and taking supplements containing high doses of vitamin C (1000mg or above)

Characteristics	Any dose(y/n) OR(95% CI)*	P value	>=1000mg (y/n) OR(95% CI)*	P value
Age (years)†				
<45	1	0.07	1	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 and above	1.23 (1.03, 1.47)		0.91 (0.62, 1.34)	
Social class†				
High	1	0.1	1	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	0.4	1	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	0.001	1	0.09
No	1.24 (1.11, 1.39)		1.23 (0.97, 1.56)	
Body mass index (BMI kg/m^2) †				
underweight (<18)	1.03 (0.72, 1.46)		1.07 (0.53, 2.15)	
normal (18-24.99)	1	0.08	1	0.6
overweight (25-30)	0.90 (0.82, 0.99)		0.87 (0.69, 1.09)	
Obese (>30)	0.93 (0.80, 1.07)		1.11 (0.81, 1.54)	
Smoking status†				
Never smoked	1	0.4	1	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	0.1	1	0.001
No	1.07 (0.98, 1.17)		1.37 (1.12, 1.67)	
Physical activity†				
No weekly physical activity	1	<0.001	1	0.008
Light moderate most weeks	1.16 (0.95, 1.41)		0.94 (0.60, 1.48)	
Vigorous 1-2/week	1.18 (0.96, 1.46)		0.98 (0.61, 1.57)	
Vigorous >=3/week	1.52 (1.23, 1.89)		1.36 (0.85, 2.19)	

Portions of red meat eaten per week[†]				
None	1	<0.001	1	<0.001
1-3	0.79 (0.72, 0.87)		0.68 (0.55, 0.85)	
4 or more	0.61 (0.54, 0.68)		0.48 (0.35, 0.65)	
Portions of fruit and veg eaten per day[†]				
<=2	1	<0.001	1	0.01
3-5	1.21 (1.08, 1.37)		1.11 (0.84, 1.48)	
More than 5	1.45 (1.26, 1.67)		1.40 (1.02, 1.92)	
Number of visit to doctors in last 12mths[†]				
None	1	<0.001	1	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 visit to alternative practitioner in last 12mths[†]				
None	1	<0.001	1	<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	10161		10161	

[*] Mutually adjusted for the other variables listed above, OR =Odds ratio

[†] p for trend given

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

		Any Dose(y/n): N=4242 (34%)		>=1000mg(y/n): 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	7,259	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	3,629	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	2,370	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	5,227	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	2,066	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	1,608	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	1,300	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 portions, total fruit and vegetable portions.

†Total numbers with history of cancer

Table 3 Odds ratios of taking supplements containing vitamin C for a range of doses for UKWCS women who self-reported a personal history of cancer or a family history of breast cancer

	Regular vitamin C doses greater or equal to							
		250mg(y/n)		500mg(y/n)		1000mg(y/n)		2000mg(y/n)
		OR(95% CI)*		OR(95% CI)*		OR(95% CI)*		OR(95% CI)*
	n†	N=1,448 (12%)	*n*†	N=1,195(10%)	*n*†	N=579 (5%)	*n*†	N==92(1%)
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 portions, total fruit and vegetable portions. 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 Odds ratios of taking supplements containing vitamin C: any dose; or 1000mg or more for UKWCS women who self-reported a family history or personal history of other illnesses

		Any dose		>=1000mg(y/n)	
		Unadjusted	Adjusted*	Unadjusted	Adjusted*
Type of illness	n	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)
Personal history					
CVD related disorders	3,217	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 bp	2,302	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	1,246	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	4,716	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	1,650	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	2,716	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	3,391	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					
CVD related disorders	9,765	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	5,558	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	2,982	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	3,799	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 bp	4,358	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	1,185	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	2,320	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	3,102	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	1,821	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	1,007	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	5,165	1.20 (1.12, 1.30)	1.19 (1.10, 1.30)	1.12 (0.95, 1.33)	1.09 (0.90, 1.31)

[*]Adjusted for BMI, age, social class, marital status, no children, smoking status, level of physical activity, low alcohol consumption, red meat portions, total fruit and vegetable portions.

CDV= cardiovascular disease

IBS= Irritable bowel syndrome

bp=blood pressure