General supplement use, subsequent use and cancer risk in the UK Women's Cohort Study

Running title: Supplement use and cancer risk in UK women

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Abstract

Background/Objectives: To determine whether general dietary supplement use is associated with cancer risks in UK women; to estimate risks relating to use at one and at two recording points.

Subject/Methods: Cox's proportional hazard regression models were used to estimate cancer risks for 32 665 middle-aged women in the UK Women's Cohort Study (UKWCS) relating to any current supplement use recorded by baseline questionnaire. During a median follow-up of 15 years there were 3 936 registered cancer incidences, including 1 344 breast, 429 smoking-related and 362 colorectal cancers. Cancer risks for 12 948 of these women, who also completed questionnaires on average 4.4 years later, were estimated in relation to any supplement use at both time points (1 527 cancers, including 561 breast, 131 smoking-related and 141 colorectal cancers). Adjustments were made for baseline confounders.

Results: Total smoking-related cancers were associated with baseline supplement use (HR=1.41; 95% CI: 1.10, 1.81) compared to non-use, but not associated with use at both recording points (HR=1.29; 95% CI: 0.78, 2.13) compared to use at neither. There was no evidence of associations between total, colorectal or breast cancers and baseline supplement use, or use at both recording points. In sub-analyses, no significant associations with breast cancer were found for pre-menopausal or post-menopausal baseline users, or similarly for use at both points (HR=1.35; 95% CI: 0.91, 2.01 and HR=0.93; 95% CI: 0.68, 1.26 respectively).

Conclusion: There was evidence that general supplement use was associated with increased smoking-related cancer risk, but no evidence of associations with total, colorectal and breast cancers.

Key Words: Dietary supplements, Cohort studies, cancer, breast cancer

Introduction

A large proportion of UK women take supplements; 41% of women in the 2008/9 National Diet and Nutrition Survey reported using supplements in the previous year.[1] Some women may take supplements to reduce their risk of chronic diseases.[2] However, the 2007 World Cancer Research Fund (WCRF) review clearly states that supplements are not recommended for cancer prevention, and reports no convincing evidence from their systematic reviews that specific micronutrients in supplement form protect against the risk of developing cancers that affect women.[3] Furthermore, increased lung cancer risks were found for smokers who used high-dose β-carotene supplements.[4, 5]

Supplementation with a variety of micronutrients may not be protective either; a meta-analysis of Randomised Control Trials (RCTs) showed no association between multivitamin supplement use and cancer mortality.[6] Nevertheless, multivitamin use has recently been reported to reduce total cancer risk in men in a large US RCT;[7] men, though, tend to have lower baseline antioxidant status than women indicative of a poorer diet.[8] Two large US cohort studies reported no association between multivitamin supplement use in women and total cancer incidence, or cancer at the major sites such as breast, colorectal and lung.[9, 10] Ten year, long-term use of multivitamins, which contain low-dose micronutrients, was also not associated with lung cancer in the Vitamins and Lifestyle (VITAL) cohort study.[11] High-dose users tend to take a number of supplement types,[12] and therefore are likely to supplement with a range of micronutrients. However, the majority of previous research has analysed risks relating to single supplements rather than multiple or general supplement use.

Although RCTs are less prone to bias than observational studies, supplementation over the intervention period may be insufficient to affect long-term risks, and these periods are usually

substantially shorter than follow-up periods in most prospective observational studies. Additionally, unlike drug trials, members of control groups can easily obtain supplements. On the other hand, it is possible that the sporadic nature of supplement use in free-living populations, as highlighted in European Prospective Investigation into Cancer (EPIC)-Heidelberg,[13] might explain lack of associations or inconsistencies in results in cohort studies. However, only the analyses of the EPIC-Heidelberg cohort and a Japanese cohort study have assessed whether general supplement use at more than one recording point was associated with cancer incidence,[14] or with cancer mortality,[15] and no associations were found for users who took supplements at more than one recording point. However, there was evidence from these cohorts that users at more than one recording point had a healthier diet compared to past and new users as well as non-users.[13, 14]

This study prospectively analyses the relationship between current use of any supplement type and total cancers, smoking-related cancers,[16, 17] colorectal and breast cancer risk in UK women. In secondary analyses the cancer risks for women using supplements at two recording points, and the risks for use at only one of these points, are compared with the risks for women not taking supplements at either point. Additionally, characteristics of UK women in these different supplement user groups are compared.

Materials and Methods

Study population

UKWCS recruitment data was gathered between1995-1998 from 35 367 women aged between 33 and 74 years old who completed a 217-item validated food frequency questionnaire (FFQ).[18] [19, 20] 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.[18] At recruitment 34 958 (99%) provided information about whether or not they took supplements.

Women with any prevalent malignant cancers recorded in UK cancer registries before baseline cohort entry were excluded. This provided 32 665 women for the risk analysis which compared women who took supplements at baseline with those that did not. Over the median follow-up period of 15 years there were 3 936 malignant cancer incidences (including non-melanoma skin cancers) ascertained from UK cancer registries via the UK Office of National statistics (ONS). These included 1 344 breast and 362 colorectal cancers diagnosed by the censor date 01/10/2011. There were also 429 smoking-related cancers[16, 17] (lung (172), cervical (27), bladder (53), kidney (48), oesophageal (47), stomach (24) and pancreas (66)).

To explore the stability of general supplement use between two survey points, further secondary analyses were undertaken for 12 948 of the above women who also completed supplement questions on the UKWCS second survey between two and five years after baseline (4.4 years on average). These women were split into three categories. 'Users at both' were defined in these analyses as women who were taking any type of supplement at both the baseline and the second survey. 'New/past users' reported taking supplements at only one of the two survey time points and 'never-users' reported no supplement use at either. Over a median follow-up of 15 years from baseline there were 1 527 incident cancers in total and 561 incident breast, 131 smoking-related and 141 colorectal cancers registered to censor date 01/10/2011 in these 12 948 women. One hundred and forty eight (26%) of the 561 breast cancer cases and 308 (20%) of the 1 527 total cancer cases occurred between baseline and the second survey in the UKWCS.

Data collection

General supplement use at baseline was determined by questionnaire using self-reported yes/no answers to:

Do you take any vitamins, minerals, fish oils or other food supplements?

General supplement use at the second survey was determined by questionnaire using self-reported yes/no answers to:

Do you presently use any dietary supplements?

Supplements were defined on this second survey questionnaire as vitamins, minerals, fibre, fish oils or other food supplements. Additionally, if participants did not answer yes to the above questions but provided details of any type of supplements taken, regardless of amount taken, then these women were designated as being general supplement users. The most popular supplement types taken daily were determined at this second survey where women were asked to indicate the frequency of types they took from a list of 16 types provided on the questionnaire.

Covariates were derived from the health and lifestyle part of the baseline questionnaire except for total alcohol intake and total energy intake which were derived from the baseline FFQ.

Statistical analyses

Characteristics of women in the different supplement use categories were described using means and percentages. Significant differences between means of baseline users and non-users were established using t-tests and significant differences between categories were established using chi squared tests. Any significant trends across groups from ‘never-users’ to ‘new/past users’ to ‘users at both’ were determined using linear regression followed by tests for linear hypotheses for means, or using chi squared tests for trend for dichotomous variable percentages.

Cox proportional hazards regression was used to provide hazard ratios to estimate cancer risks in relation to supplement use for women in the UKWCS. The reference group in the main analyses were 'non-users' at baseline, whereas in the secondary analyses cancer risks for 'users at both' and 'new/past users' categories were compared to 'never-users'. Probability weighting was used to produce estimated average risks representative of the UK population of women: needed because of the recruitment of substantially higher proportions of vegetarians and fish eaters into the cohort compared to the UK population. Vegetarians and fish eaters were weighted by 0.27 and 0.43 respectively. Adjustments were made in the total cancers, smoking-related cancers and colorectal cancer analyses for age; BMI (underweight, normal, overweight, obese); education (none, up to degree level, degree); smoking status (never, past, current occasionally, current every day), minutes sweating exercise per week; alcohol intake (g/day); total energy intake (kcal/d) and dietary type (mainly meat, oily fish, other fish eater, vegetarian as described elsewhere[18]). In addition to the above, the breast cancer analyses were adjusted for contraceptive pill use (never, past, current); Hormone Replacement Therapy (HRT) (never, past, current); age at menarche, and parity, but not smoking status. Although there was no interaction between supplement use at baseline and menopausal status in relation to breast cancer risks in likelihood ratio tests for interactions, hazard ratios were examined by menopausal status, as commonly practised in breast cancer risk analyses. Menopausal status at baseline was determined from responses to a number of questions relating to last natural period, HRT and contraceptive pill use, hysterectomy and ovary removal.[21] Sensitivity analyses were undertaken to make additional adjustments for family history of cancer in first degree relatives (missing data was >5%) and in the breast cancer analysis for estimated weeks of breastfeeding. Other sensitivity analyses excluded incident cancers within two years of baseline. Further sensitivity analysis, with a median follow-up time of 10.6 years, was undertaken relating to use at two time points where the time-to-event calculation was started from the second survey date instead of from baseline, thereby excluding incident cases diagnosed between the

surveys. Analyses were carried out using Stata version 12 (Timberlake Consultants UK, London, UK) and results were based on a significance level of $P<0.05$.

Results

Of the 32 665 eligible women, 62% were supplement users at baseline and 54% of the 12 948 women at the second survey had taken supplements at both recording points, and were classed as users at both. At the second survey 25% were new/past users (had taken supplements at either recording point but not at both) and 21% were never-users. Of the 8 915 (69%) women who were currently taking supplements at the second survey, 7010 (79%) had also taken supplements at baseline and were classed as users at both. On the second survey questionnaire 27% of all women reported taking fish oils, 25% multivitamins/minerals, 19% primrose/starflower oil, 18% vitamin C and 14% calcium supplements on a daily basis. These were the most popular named supplement types, and for each of these there were statistically significant differences in intake between menopausal statuses: multivitamins and primrose/starflower oil were more likely to be used by pre-menopausal women, whereas cod liver oil and the others were more likely to be taken by women of post-menopausal age.

There were statistically significant differences between general supplement users and non-users at baseline for the majority of characteristics listed in table 1. In particular, users reported a higher fruit and vegetable intake, a lower meat intake, lower alcohol intake and reported doing more vigorous exercise than non-users. Users were also more likely to have a family history of any cancer. However, there were no significant differences in level of education.

Similarly as observed in table 2, there were increasingly healthier behaviours relating to exercise, alcohol use and fruit and vegetable intake, meat intake from never-users (at baseline and second survey), through new/past users, to users at both. There was a decreasing trend for

HRT use, number of children and estimated cumulative breast feeding, but an increase in trend for supplement use for ex-smokers. However, there were no significant differences between user frequency in relation to family history of cancer.

As observed in table 3 in the analysis of supplement use assessed at baseline for all women there was no statistically significant difference in total cancers, colorectal or breast cancer risk between all supplement users and non-users either in the unadjusted or adjusted analyses (adjusted HR=1.06; 95% CI: 0.98, 1.14, HR=1.13; 95% CI: 0.87, 1.46 and HR=1.01; 95% CI: 0.89, 1.15 respectively). There was no evidence of interactions between supplement use and menopausal status (p=0.13) or HRT use on breast cancer risk. Furthermore in the sub-analysis by menopausal status, hazard ratios were not statistically significant: (adjusted HR=0.96; 95% CI: 0.81, 1.13 and HR=1.07; 95% CI: 0.88, 1.30 for post-menopausal women and pre-menopausal respectively as shown in table 3). However, an association was found for smoking-related cancers (HR=1.41; 95% CI: 1.10, 1.81, p=0.007) which remained after excluding cancers occurring within 2 years of the baseline (HR=1.36; 95% CI: 1.05, 1.76, p=0.02).

Similarly in the secondary analysis exploring consistency of supplement-taking between baseline and the second survey, compared to never-users there was no significant differences in risks of total cancers, colorectal and breast cancer in the adjusted analyses for new/past users (HR=0.96; 95% CI: 0.81; 1.14, HR=0.71; 95% CI: 0.40, 1.26; and HR=0.98; 95% CI: 0.73, 1.30 respectively), and users at both (HR=1.01; 95% CI: 0.88, 1.17; HR=1.00; 95% CI: 0.63; and HR=1.08; 95% CI: 0.85, 1.38 respectively) as observed in table 4. Although the point estimates were raised in the pre-menopausal sub-analysis they were not statistically significant (HR=1.17; 95% CI: 0.74, 1.84 and HR=1.35; 95% CI: 0.91, 2.01 respectively for past/new users and users at both). Additionally, no evidence of associations was found for smoking-related cancers for past/new users (HR=0.97 95%CI: 0.53, 1.79) or for users at both (HR=1.29; 95% CI:

0.78, 2.13). Additional adjustment for estimated cumulative breast feeding duration in the breast cancer analyses and for family history of cancer had little effect on hazard ratios and confidence intervals in the above analyses.

The results of the sensitivity analysis which excluded cases diagnosed within two years of baseline or diagnosed between supplement-taking surveys did not affect the overall conclusion of this research (data not shown).

Discussion

There was little evidence of associations between general supplement use and total cancers, colorectal and breast cancer risk in this UK cohort, whether comparing risks for supplement users at one recording point with non-users or comparing risk for users at two recording points with never-users or comparing past/new users with never users. There was evidence that general supplement use was associated with increased smoking-related cancer risk in the full sample baseline analysis. However, this was not significant for the users at both recording points, but this secondary analysis was limited by lower numbers and therefore lower power. There was evidence, however, that users at both recording points had different characteristics from women who had not used supplements at one or both points.

Descriptive results from these UKWCS analyses support the inverse supplement hypothesis that supplement users lead a healthier lifestyle than non-users, as found in the UK,[22-24] and elsewhere.[25-30] In particular, supplement users in the UKWCS had on average a higher intake of fruit and vegetables, a lower intake of meat and alcohol, and also spent more time exercising vigorously, and had lower BMIs. Moreover, the results show a trend towards these healthier behaviours from never-users, new/past users to users at both. Similarly, women taking

supplements at all three recording points in the EPIC-Heidelberg cohort in Germany, classed as 'consistent users', had the highest intake of dairy products, fish, fruit and vegetables and wine, the highest physical activity but the lowest intake of meat compared to the other categories, producing trends for all but physical activity.[13] In the cohort of Japanese women, 'consistent users' had lower BMIs and consumed significantly larger amounts of fruits, folate and vitamin C than the other categories, but were more likely to be regular alcohol drinkers and exercised less, additionally there were no significant trends for green vegetables, meat and fish intake.[14] In these previous studies, unlike the current study, ex-smokers were more likely to be inconsistent users. Trends in HRT or contraceptive pill use were found in the current study, but were not examined in the previous studies.

The increased risk in smoking-related cancers in the baseline analysis, found after adjustment for confounders, may relate to evidence that high-dose β-carotene is associated with increased lung [4, 5] and other smoking-related cancer risks in smokers.[31] Conversely, β-carotene has also been inversely associated with smoking-related cancer risks in non-smokers.[31] Potentially, β-carotene may act as a pro-oxidant or antioxidant depending upon the biological environment.[32] Unfortunately, the amount of β-carotene taken in supplements by the UKWCS users in the current analyses was not reported by questionnaire and is unknown, though is usually present in low doses in popular multivitamin supplements.[33] Furthermore, since only 11% of the women smoked, numbers were considered too low to power sub-analyses by smoking status in relation to general supplement use. Alternatively, the increased risks found in the main analysis may be due to other micronutrients in supplements, confounding or multiple testing. The lack of association for smoking-related cancers for users at the two recording points in the UKWCS does not support the main analysis finding; this may be due, however, to fewer cases and shorter follow-up time from use at the second survey in this secondary analysis.

There was no evidence of significant associations between general supplement use at baseline and later incidences of total cancers, colorectal or breast cancer for all women, or when explored by menopausal status in the breast cancer analysis. This is in line with results from a breast cancer meta-analysis,[34] and also results from two large cohort studies which reported no associations between multivitamin use in women and total cancers, colorectal or breast cancer, as well as lung cancer incidence.[9, 10] There is some prior evidence, however, that folic acid in multivitamins is associated with reduced risk of early stages of colorectal cancer.[35] The breast cancer results support those from two Danish and US case–control studies on general supplement use;[36, 37] however, they are in contrast to a Taiwanese case–control study where general supplement use was associated with a reduced risk of breast cancer (OR=0.40, 95% CI: 0.3, 0.7).[38] Selection and recall bias, which can occur in case-control studies, possible lower dietary intakes of micronutrients in the Taiwanese women or the nature of the supplements taken could account for discrepancies in results.

Additionally, there were no associations between reporting supplement use at two recording points (both baseline and second survey) and total cancers, colorectal or breast cancer risk for all women, and by menopausal status in the breast cancer analysis. The current study is the first to analyse cancer risks for UK women reporting supplement use at more than one time point in comparison to never-users. Previously, only two studies had analysed general supplement use at more than one recording point in relation to cancer, reporting no associations for 'consistent users' in relation to total cancer and major site-specific cancers in a Japanese cohort incidence, and total mortality in the German EPIC-Heidelberg cohort.[14, 15]

Major strengths of the UKWCS study are the prospective design and the large number of cancer cases, particularly in the baseline analysis. However, the power to detect associations was substantially reduced in the analysis of users at two recording points, though numbers in this category were larger (7 010 (54%)) compared with previous studies (German men and women: 3 559 (18%) ; Japanese women: 1962 (5.8%)),[14, 15]. Another limitation of this secondary analysis in the UKWCS is that within the category of 'users at both' it was not possible to distinguish between regular users who took any supplements several days each week and sporadic users. Misclassification of sporadic users in the UKWCS into this 'users at both' category for pre-menopausal women, for instance, would have attenuated risks in this category, if cancer risk were lower for sporadic users. However, the questions relating to regular intake, used to define consistent use in the two previous studies, [14, 15] indicate the women in this group in those studies were more likely to be stable longer-term users. The average period between baseline and final supplement use recordings was also shorter in the UKWCS. A limitation in the current and previous studies is that it was unknown whether the same types of supplements were taken at baseline as those at follow-up surveys: it was unknown for how long, how frequently, how many and at what doses supplements were taken.

Although supplement use in nutrient deficient populations may be required to reduce the development of cancer,[39] any protective effects of general supplement use *per se* on cancer risk in well-nourished populations such as the UKWCS would be more difficult to explain biologically. As previously reported, many of the UKWCS took a variety of supplement types.[12] In line with findings from a small 2008 UK national survey,[40] at the UKWCS second survey cod liver oil was more likely to be taken by women of post-menopausal age, whereas multivitamins were more likely to be used by younger women. Whether or not these supplement types have different associations with breast cancer risk, differences in estimates between menopausal statuses in the current analyses were not significant, neither were the increased risk estimates across use

categories for pre-menopausal women significant. Further research is needed into pre-menopausal users, particularly with larger sample sizes, as research is lacking in this area.

While observational data such as these are only able to highlight links between diet and disease incidence rather than provide causal evidence, the apparent lack of benefit associated with general supplement use on cancer risks shown in this UK cohort lends support to the guidelines produced by the World Cancer Research Fund that supplement-taking is not advised for reducing cancer risk.

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Table 1 **Characteristics of all supplement users and non-users at baseline in the UKWCS**

	Non-users N=12495 (38%)	Users N=20170 (62%)	Difference in mean (95% CI)	p
Age (years) mean (sd)	51.6 (9)	52.4 (9)	-0.78 (-0.99,-0.57)	<0.001
Weight (kg) mean (sd)	66.6 (12)	65.0 (12)	1.57 (1.30, 1.84)	<0.001
BMI (kg/m^2) mean (sd)	24.8 (4)	24.2 (4)	0.63 (0.53, 0.73)	<0.001
Age at menarche (years)	12.8 (2)	12.8 (2)	-0.04 (-0.07, 0.00)	0.04
Parity mean (sd)	1.92 (1.3)	1.82 (1.3)	0.09 (0.06, 0.12)	<0.001
Est cumulative breast feeding (weeks)	25.1 (37)	22.8 (34)	2.28 (1.49, 3.06)	<0.001
Vigorous exercise (mins/d) mean (sd)	14.0 (28)	15.9 (30)	-1.86 (-2.53,-1.20)	<0.001
Total energy intake (kcal/d) mean (sd)	2338 (827)	2373 (767)	-34.8 (-52.4,-17.1	<0.001
Alcohol intake (g/day) mean (sd)	9.0 (11)	8.5 (10)	0.50 (0.27, 0.73)	<0.001
Total meat intake (g/day) mean (sd)	73.6 (69.1)	60.1 (64.1)	13.5 (12.0, 14.9)	<0.001
Total fruit & veg (g/day) mean (sd)	596 (364)	656 (369)	-60.4 (-68.6,-52.2)	<0.001
Dietary type n (%)				<0.001
Mainly Meat eater	9311 (74.5)	13429 (66.6)		
Oily Fish eater	198 (1.6)	603 (3.0)		
Other fish eater	916 (7.3)	2135 (10.6)		
Vegetarian	2070 (16.6)	4003 (19.9)		
Never smoked n(%)	7116 (58.5)	11288 (57.7)		0.2
Ex-smoker n(%)	3540 (29.1)	6211 (31.8)		<0.001
Never used HRT n(%)	8527 (70.1)	13079 (66.5)		<0.001
Never used pill n(%)	3884 (31.5)	6458 (32.8)		0.01
Socio-economic status n(%)				0.8
Higher	4807 (39.1)	7743 (39.0)		
Middle	5201 (42.4)	8463 (42.7)		
Lower	2276 (18.5)	3621 (18.3)		
Education level n(%)				0.1
No qualifications	2110 (16.9)	3395 (16.8)		
Non-degree qualifications	7151 (57.2)	11759 (58.3)		
Degree	3234 (25.9)	5016 (24.9)		
Family history of any cancer n(%)	4491 (38.2)	7546 (39.8)		0.007
Family history of breast cancer n(%)	872 (7.4)	1459 (7.7)		0.4

Table 2 Baseline characteristics of women in the UKWCS according to supplement use at baseline and second survey for never users; past/new users and users at both

	Never[1] users N=2765 (21%)	Past/new[2] users N=3173 (25%)	Users at both[3] N=7010 (54%)	P value for trend
Age (years) mean (sd)	52.1 (9)	51.2 (9)	52.6 (9)	<0.001
Weight (kg) mean (sd)	65.4 (12)	65.4 (12)	64.0 (11)	<0.001
BMI (kg/m^2) mean (sd)	24.5 (4)	24.4 (5)	23.9 (4)	<0.001
Age at menarche (years) mean (sd)	12.8 (2)	12.8 (2)	12.8 (2)	0.2
Parity mean (sd)	1.92 (1.3)	1.86 (1.3)	1.82 (1.3)	0.004
Cumulative breast feeding (weeks)	28.4 (39)	26.1 (37)	24.4 (35)	<0.001
Vigorous exercise (mins/d) mean (sd)	13.4 (27)	13.9 (23)	16.6 (31)	<0.001
Total energy intake (kcal/d) mean (sd)	2362 (851)	2380 (763)	2371 (727)	0.7
Alcohol intake (g/day) mean (sd)	9.0 (11)	8.6 (10)	8.1 (10)	<0.001
Total meat intake (g/day) mean (sd)	69.0 (78.0)	61.0 (62.3)	53.1 (57.1)	<0.001
Total fruit & veg (g/day) mean (sd)	614 (425)	630 (341)	678 (359)	<0.001
Dietary type n (%)				<0.001
Mainly Meat eater	1966 (71.1)	2098 (66.1)	4395 (62.7)	
Oily Fish eater	45 (1.6)	63 (2.0)	212 (3.0)	
Other fish eater	212 (7.7)	323 (10.2)	787 (11.2)	
Vegetarian	542 (19.6)	689 (21.7)	1616 (23.1)	
Never smoked n(%)	1712 (63.0)	1889 (60.9)	4181 (61.1)	0.1
Ex-smoker n(%)	734 (27.2)	934 (30.1)	2089 (30.6)	0.002
Never used HRT n(%)	1955 (72.2)	2161 (69.6)	4498 (65.3)	<0.001
Never used pill n(%)	940 (34.3)	898 (28.5)	2300 (33.1)	0.9
Socio-economic status n(%)				0.8
Higher	1133 (41.5)	1293 (41.3)	1829 (40.9)	
Middle	1136 (41.6)	1299 (41.5)	2945 (42.6)	
Lower	463 (17.0)	540 (17.2)	1143 (16.5)	
Education level n(%)				<0.001
No qualifications	381 (13.8)	366 (11.5)	984 (14.0)	
Non-degree qualifications	1530 (55.3)	1858 (58.6)	4120 (58.8)	
Degree	854 (30.9)	949 (29.9)	1906 (27.2)	
Family history of any cancer n(%)[4]	1030 (39.3)	1181 (39.6)	2711 (41.3)	0.06
Family history of breast cancer n(%)[4]	208 (7.9)	228 (7.6)	537 (8.2)	0.6

[1]Never users: women who reported no supplement use at baseline and at second survey

[2]Past/new users: women who reported supplement use on only one questionnaire, either at baseline and at second survey

[3]Users at both: women who reported supplement use at both baseline and at second survey

[4]family history of cancer in first degree relatives

Table 3 Cancer risks for all supplement users at baseline in the UKWCS compared to non-users (N=32665)

Any supplement use at baseline	Cases/ Non-cases	Unadjusted HR (95% CI)	Adjusted[1,2] HR (95% CI)
Total cancers			
Non-users	1459/11036	1	1
Users	2477/17693	1.06 (0.99,1.14)	1.06 (0.98,1.14)
Smoking related cancers			
Non-users	146/12349	1	1
Users	283/19887	1.22 (0.99, 1.51)	1.41 (1.10, 1.81)
Colorectal cancer			
Non-users	130/12365	1	1
Users	232/19938	1.17 (0.93, 1.46)	1.13 (0.87, 1.46)
Breast cancer all women			
Non-users	502/11993	1	1
Users	842/19328	1.03 (0.92,1.16)	1.01 (0.89,1.15)
Breast cancer post-menopausal women			
Non-users	288/5927	1	1
Users	481/10285	0.96 (0.82,1.11)	0.96 (0.81,1.13)
Breast cancer pre-menopausal women			
Non-users	214/6066	1	1
Users	361/9043	1.13 (0.94,1.35)	1.07 (0.88,1.30)

[1]All cancer, smoking-related cancer and colorectal cancer analyses adjusted for baseline covariates: age, BMI, education, hrs exercise sweating per week, alcohol intake, total energy intake, smoking habit, diet type

[2]Breast cancer analysis adjusted for baseline covariates: age, BMI, education, hrs exercise sweating per week, alcohol intake, total energy intake, diet type, parity, age at menarche, contraceptive pill use, HRT use

Table 4 Cancer risks for users at both, and for past/new users compared to never-users according to any supplement use at baseline and second survey in the UKWCS (N=12948)

Any supplement use at baseline or second survey	Cases/ Non-cases	Unadjusted HR (95% CI)	Adjusted[1,2] HR (95% CI)
Total cancers			
Never users at both	334/2431	1	1
Past/new users	343/2830	0.88 (0.75, 1.04)	0.96 (0.81,1.14)
Users at both	850/6160	1.01 (0.89, 1.16)	1.01 (0.88,1.17)
Smoking related cancers			
Never users at both	27/2738	1	1
Past/new users	27/3,146	0.78 (0.44,1.37)	0.97 (0.53,1.79)
Users at both	77/6,933	1.10 (0.70,1.75)	1.29 (0.78,2.13)
Colorectal cancer			
Never users at both	35/2730	1	1
Past/new users	27/3145	0.62 (0.36,1.07)	0.71 (0.40,1.26)
Users at both	79/6931	0.95 (0.62,1.44)	1.00 (0.63,1.57)
Breast cancer all women			
Never users at both	110/2655	1	1
Past/new users	132/3041	1.03 (0.79, 1.34)	0.98 (0.73,1.30)
Users at both	319/6691	1.13 (0.90,1.42)	1.08 (0.85,1.38)
Breast cancer post-menopausal			
Never users at both	71/1379	1	1
Past/new users	71/1427	0.95 (0.67,1.33)	0.90 (0.62,1.31)
Users at both	189/3619	1.00 (0.75,1.32)	0.93 (0.68,1.26)
Breast cancer pre-menopausal			
Never users at both	39/1276	1	1
Past/new users	61/1614	1.25 (0.81,1.94)	1.17 (0.74,1.84)
Users at both	130/3072	1.40 (0.95,2.08)	1.35 (0.91,2.01)

[1]All cancer, smoking-related cancer and colorectal cancer analyses adjusted for baseline covariates: age, BMI, education, hrs exercise sweating per week, alcohol intake, total energy intake, smoking habit, diet type

[2]Breast cancer analysis adjusted for baseline covariates: age, BMI, education, hrs exercise sweating per week, alcohol intake, total energy intake, diet type, parity, age at menarche, contraceptive pill use, HRT use