British Journal of Nutrition (2023), 129, 1543–1551 doi:10.1017/S0007114522000447

Association of tea-drinking habits with the risk of non-Hodgkin lymphoma: a prospective cohort study among postmenopausal women

Zikun Wang[1], Rhonda Arthur[2], Aladdin H. Shadyab[3], Nazmus Saquib[4], Karen C. Johnson[5], Linda G. Snetselaar[6], Lina Mu[7], Zhongxue Chen[1]* and Juhua Luo[1]

[1]*Department of Epidemiology and Biostatistics, School of Public Health, Indiana University Bloomington, Bloomington, IN, USA*
[2]*Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA*
[3]*Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, CA, USA*
[4]*Department of Research, College of Medicine, Sulaiman AlRajhi University, Al Bukayriyah, Kingdom of Saudi Arabia*
[5]*Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN, USA*
[6]*Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA, USA*
[7]*Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, Buffalo, NY, USA*

(Submitted 29 July 2021 – Final revision received 6 January 2022 – Accepted 31 January 2022 – First published online 10 February 2022)

Abstract

Although biological evidence suggests that tea consumption may protect against non-Hodgkin lymphoma (NHL), epidemiological evidence has been unclear. The aim of this study was to examine the association between tea-drinking habits and the risk of NHL in a large nationwide prospective cohort of postmenopausal US women. 68 854 women who were enrolled from 1993 through 1998 in the Women's Health Initiative Observational Study and responded to year 3 annual follow-up questionnaire comprised the analytic cohort. Newly diagnosed NHL cases after the year 3 visit were confirmed by medical and pathology reports. Multivariable-adjusted Cox proportional hazards models were performed to assess the associations of tea-drinking habits (specifically, the amounts of caffeinated/herbal/decaffeinated tea intake) with the overall risk of NHL and three major subtypes (diffuse large B-cell lymphoma (*n* 195, 0·3 %), follicular lymphoma (*n* 128, 0·2 %) and chronic lymphocytic leukaemia/small lymphocytic lymphoma (*n* 51, 0·1 %)). Among 62 622 participants, a total of 663 (1·1 %) women developed NHL during a median follow-up of 16·51 (SD 6·20) years. Overall, different amounts of type-specific tea intake were not associated with the risk of NHL regardless of its histologic subtypes after adjustment for confounders. Our findings suggest that tea intake at the current consumption level does not influence the risk of NHL, regardless of its histologic types.

Key words: Herbal tea: Teas: Diffuse large B-cell lymphoma: Follicular lymphoma: Small lymphocytic lymphoma: Chronic lymphocytic leukaemia

Non-Hodgkin lymphoma (NHL) accounts for approximately 4·2 % of all cancer diagnoses, and about 720 000 people are living with NHL in the USA. Based on the estimate from the American Cancer Society, around 81 560 people are projected to be diagnosed with NHL in 2021[(1)]. In addition, the incidence of NHL substantially increased in 1970 and then stabilised[(2)]. However, the risks vary considerably in subtypes of NHL; in particular, the occurrence of diffuse large B-cell lymphoma remained stable, whereas the incidence of indolent B-cell lymphomas and T-cell NHL greatly rose from 1989 to 2007[(3)].

Studies have revealed that NHL cases were more likely to be diagnosed at older ages[(4)] among White people in the USA[(5)] Moreover, chronic inflammation[(6)], including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)[(7)], is a known risk factor for NHL overall, except for certain subtypes of NHL. In addition, family history of any cancer is one of the established risk factors for NHL[(6)]. Besides, studies indicate that lifestyle factors such as smoking[(8)], higher alcohol consumption[(9)] and lack of physical activity (PA)[(10)] are adverse risk factors for certain NHL subtypes. However, the aetiology of most of the

Abbreviations: NHL, non-Hodgkin lymphoma; PA, physical activity; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T2DM, type 2 diabetes mellitus; WHI-OS, Women's Health Initiative Observational Study.

* **Corresponding author:** Zhongxue Chen, email zc3@indiana.edu

cases of NHL is largely unexplored[6]. Thus, identifying modifiable risk factors for NHL is critical for NHL prevention.

Tea (Camellia sinensis; Theaceae) is one of the most popular beverages worldwide and is recognised as an antioxidant drink because of its wealth of bioactive compounds, leading to intense antioxidant activity in the body[11]. Traditionally, tea is defined by their formation process; for example, green tea is unfermented and black tea is completely fermented. At present, teas have been hypothesised to be associated with the risk of developing cancers, such as colorectal cancer, urinary tract cancer and NHL[12–19]. The beneficial impacts of tea are derived from diverse bioactive compounds, including flavonoids, L-theanine, theaflavins, caffeine, catechins, etc. Specifically, evidence from *in vivo* and *in vitro* studies[20–22] has indicated that the aforementioned substances could exert anticancer effects protect against various types of haematologic and solid malignancies by inhibiting angiogenesis through the inhibition of cell proliferation and through mediating apoptosis of haematologic malignancies[16]. Another major bioactive compound found in tea, caffeine (1,3,7-trimethylxanthine), has been recognised as a cancer-fighting property in humans since it can down-regulate the expression of many Wnt signalling proteins viz. cyclin D1 and apoptosis regulator Bcl-2[23]. In addition, some of these bioactive compounds in tea may act synergistically in anticancer action[20].

Thus far, epidemiological evidence on the association between tea intake and the risk of developing NHL is inconclusive[12,13,15–19,24]. A Japanese study showed that tea intake was statistically significantly related to a lower risk of NHL among male and female aged 40–79 years[16]. However, a case–control study performed in the northeastern part of Italy[24] indicated that caffeinated tea but not decaffeinated or herbal tea was positively associated with a higher risk of NHL. Other observational studies showed no associations between tea intake and risk of NHL[12,13,15,17–19]. These inconsistencies may be due to small numbers of cases, different scales to assess tea intake, different types of tea consumption or different study populations. Besides, the evidence on examining associations between tea-drinking habits and NHL subtypes has also been insufficient. On the other hand, herbal tea, made from a wide variety of dried fruits, flowers, spices or herbal infusions rather than Camellia sinensis, contains many monomeric flavonoids[25]. Despite evidence indicates that a possible beneficial association has been observed between herbal tea and solid tumour risk[26], the epidemiological evidence remains scarce for haematologic malignancies at present.

Existing evidence also suggests that the level of tea consumption and NHL risk or mortality may vary across ethnicity. Notably, tea consumption was about 8·5 times higher in Asian compared with White[27]; whereas higher risk and higher mortality rate of NHL were found among White populations, compared with Asian populations[5]. The difference in the occurrence of malignant lymphomas between different racial groups may be partly explained by tea-drinking habits. Additionally, previous findings indicate that tea protects against cigarette smoke-induced apoptosis[28]. Moreover, tea consumption is correlated with age[29], and it is related to decreased risk of obesity[30]. However, previous studies on NHL have not investigated the effect modification on tea intake by age, smoking status, alcohol consumption, BMI or racial group.

Given these mixed findings and limitations, we aimed to assess whether tea-drinking habits, such as the amount of type-specific tea intake, were associated with risks of NHL and its major subtypes among the Women's Health Initiative Observational Study (WHI-OS)[31].

Methods

Study population

The Women's Health Initiative (WHI) is a large, prospective study with long-term follow-up, which consists of three clinical trials (*n* 68 132) and an observational study (*n* 93 676). The study cohort comprised 161 808 postmenopausal women aged 50–79 who were recruited from forty clinical sites throughout the USA between 1993 and 1998. Information on the WHI design is described elsewhere[32]. All adjudicated primary cancers for observational study participants were updated through 1 March 2019. The WHI study protocol was reviewed and approved by the Fred Hutchinson Cancer Research Center (Fred Hutch) and the institutional review board at each participating institution.

Our follow-up baseline was year 3; specifically, participants were eligible for the current analyses if they responded to the year 3 follow-up questionnaire in the WHI-OS, which included information on the amount of type-specific tea intake (caffeinated/herbal/decaffeinated tea). Other information on covariates was collected from the year 3 follow-up questionnaire, except for education level, pack-years of smoking group, total energy intake, hypertension status and treatments, RA, SLE, racial or ethnic group, family history of any type of cancer and type 2 diabetes mellitus (T2DM), which were measured at WHI-OS baseline. In total, 82 568 postmenopausal women were initially included in the analysis. Moreover, we excluded women who reported any cancer history prior to annual visit year 3 (other than non-melanoma skin cancer, *n* 8819), women who died or were lost to follow-up or developed NHL before year 3 visit (i.e. women who reported NHL history at baseline WHI screening visit or who had incident NHL between WHI baseline and year 3, *n* 313) and women who had missing responses for primary exposures of interest, such as regular (caffeinated) tea intake (*n* 1651), herbal tea intake (*n* 2277) and decaffeinated tea intake(*n* 2865), the sample comprised 68 854 women. We further excluded 6232 women with missing data on the main covariate variables (racial and ethnic group (*n* 181), education levels (*n* 517), recreational PA (*n* 104), pack-years of smoking (*n* 2392), alcohol use (*n* 208), hormone therapy use for last 2 years (HRT, *n* 1341), hypertension status and treatments (*n* 1119), RA (*n* 470), SLE (*n* 815)). The final analytic cohort comprised 62 622 participants (Fig. 1).

Exposure measures

Tea-drinking habits were recorded and collected from self-administered standardised observational study questionnaires at year 3. The information addressing habitual tea intake asked

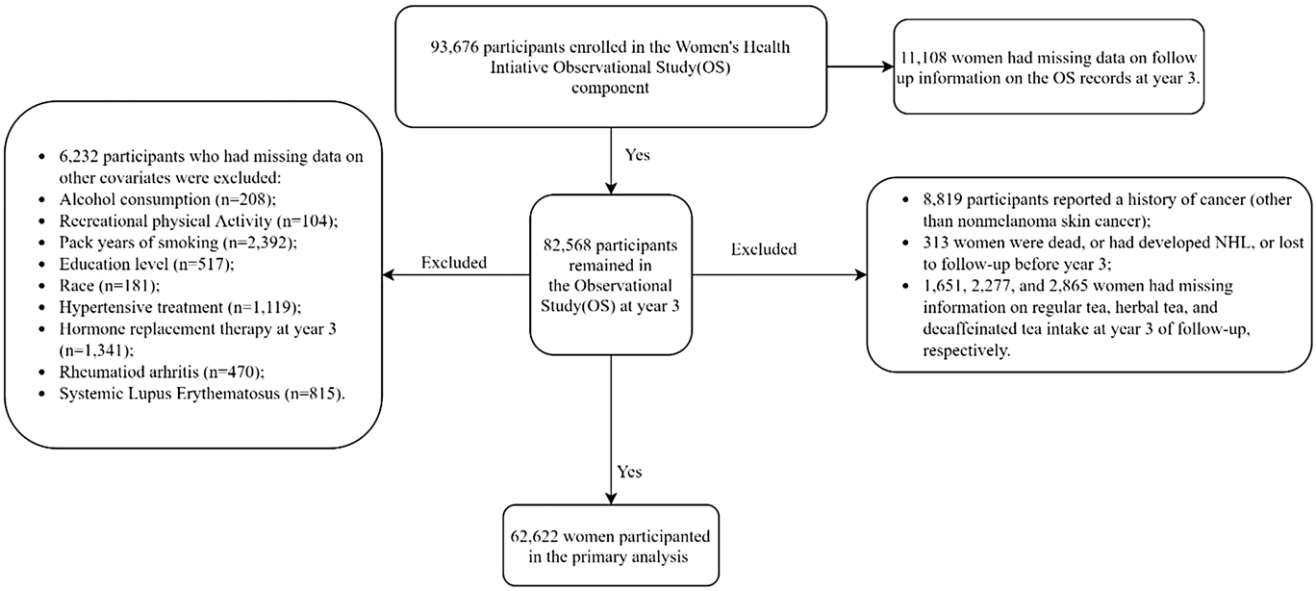

Fig. 1. Algorithm of study participants for tea intake and the risk of non-Hodgkin lymphoma.

about: 'How many cups of regular tea (not herbal, not decaf) did you drink per week in past 3 months, 'How many cups of herbal tea did you drink per week in past 3 months' and 'How many cups of decaffeinated tea did you drink per week in past 3 months'. The information on the frequency of tea-drinking was collapsed for analyses to four levels (non-drinkers, < 1 cup per week, 1–6 cups per week or ≥ 7 cups per week) (1 cup = 0·237 l) because the number of participants in the latter levels was relatively sparse. In addition, tea-drinking statuses were merged into two levels (non-drinkers, tea drinkers) for chronic lymphocytic leukaemia/small lymphocytic lymphoma in herbal tea intake and decaffeinated tea intake due to sparse data.

Outcome ascertainment

The primary outcome of interest was the incidence of NHL. In general, new NHL cases, occurring after annual visit year 3, at which time our exposure variables (tea-drinking habits) were reported, was collected. Newly diagnosed NHL patients were first identified by self-reports through mail or telephone questionnaires and third-party reports and were further confirmed by centralised trained cancer adjudicators based on medical records and pathology reports from hospitals or laboratories[33]. Women who self-reported a different diagnosis but were found upon review of medical pathology records to have NHL were considered as NHL cases. Classification and histology of tumours in the WHI were based on the Surveillance, Epidemiology, and End Results guidelines. The case morphology classification code used ICD-O-3 coding[33].

Three major subtypes of NHL were further examined in the current study, including diffuse large B-cell lymphoma (ICD-O-3 codes: 9678/3–9680/3 and 9684/3), follicular lymphoma (ICD-O-3 codes: 9690/3–9698/3) and chronic lymphocytic leukaemia/small lymphocytic lymphoma (ICD-O-3 codes: 9823/3 and 9670/3).

Follow-up duration was defined from the year 3 visit to the date of NHL diagnosis, the date of death or the last date of follow-up (1 March 2019), whichever occurred first.

Other covariates

Potential confounders[4–6,8–10] in the models included socio-demographic variables: age group (50–59, 60–69 and 70–79+), racial or ethnic group (American Indian or Alaska Native, Asian or Pacific Islander, Black or African American, Hispanic White/Latino, White (not of Hispanic origin) and other), educational level (high school diploma and below, school after high school, college degree or higher)); lifestyle risk factors: BMI group (BMI, body weight in kilograms divided by squared body height in meters: < 25 kg/m^2, 25 to < 30 kg/m^2, 30 to < 35 kg/m^2, ≥ 35 kg/m^2), total energy intake (kcal/d), alcohol use (non-drinkers or past drinkers, ≤ 3 drinks per month, 1–4 drinks per week and ≥ 5 drinks per week), pack-years of smoking (non-smokers, < 5, 5–20, ≥ 20), recreational PA (total metabolic equivalents of energy expenditures per week (MET-hours/week)[10], PA: < 5, 5–10, 10–20, 20–30 and > 30); and clinical risk factors/current medical conditions factors: hypertension status and treatment (no hypertension, untreated hypertension, treated hypertension), family history of any cancer (yes/no), hormone therapy use for last 2 years (HT: never use, oestrogen alone use, progesterone alone use, oestrogen or progesterone use, both use), RA (yes/no), SLE (yes/no) and T2DM (no diabetes, diabetes without treatment, diabetes with treatment).

Statistical analysis

Socio-demographic factors, lifestyle factors and medical conditions were examined by tea intake status. The frequencies of those selected categorical risk factors with percentage N (%) were presented. Mean and standard deviation of the selected continuous risk factors were calculated.

https://doi.org/10.1017/S0007114522000447 Published online by Cambridge University Press

Incidence rates of newly diagnosed NHL and three subtypes of NHL were estimated using person-years as the denominator (number of cases/person-years × 10 000). Cox proportional hazards regression models were applied to evaluate associations between the amount of type-specific tea intake (caffeinated/herbal/decaffeinated tea) and the risk of NHL. Moreover, associations of tea-drinking habits with risks of the three major subtypes of NHL were further examined (diffuse large B-cell lymphoma: *n* 195, 0·3 %; follicular lymphoma: *n* 128, 0·2 % and chronic lymphocytic leukaemia/small lymphocytic lymphoma: *n* 51, 0·1 %). The rest of the NHL cases (*n* 289) were considered as a heterogeneous group and were not assessed in separate analyses. To avoid confounding, age-adjusted and multivariable-adjusted models were conducted. Hazard ratios and 95 % CI are presented. In the multivariable-adjusted models, potential confounders[4–6,8–10], including age group, racial or ethnic group, education, BMI group, alcohol use, pack-years of smoking group, PA, hypertension status and treatments, family history of any cancer, HT, RA, SLE and T2DM and treatments, were adjusted. Tests for trends were performed to determine whether or not a significant dose–response effect exists by modelling the ordinal variables as continuous variables. Interactions between tea intake (caffeinated/herbal/decaffeinated tea), selected categorical covariates (age group (50–59, 60–69 and 70–79+), BMI group (< 25 kg/m^2, 25 to < 30 kg/m^2, 30 to < 35 kg/m^2, ≥ 35 kg/m^2), pack-years of smoking group (non-smokers, < 5, 5–20, ≥ 20), racial or ethnic group (White (not of Hispanic origin)/others) and alcohol use (non-drinkers or past drinkers, ≤ 3 drinks per month, 1–4 drinks per week and ≥ 5 drinks per week)) and risk of NHL were examined in the multivariable-adjusted models. Additionally, mode imputation, a popular method that replaces missing data for categorical variables with mode values of the corresponding variables, was applied to reduce bias[34]. Furthermore, we repeated the analyses for associations of tea-drinking habits (caffeinated/herbal/decaffeinated tea) with risks of NHL after excluding the first 5 years of follow-up to minimise possible reverse causality.

All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute). *P*-values were two-tailed, and *P*-values ≤ 0·05 were considered statistically significant.

Results

During a median 16·51-year follow-up (range, 0·01–21·22 years, (SD 6·20) years), 663 (1·1 %) were diagnosed with NHL among 62 622 participants.

Overall, frequent regular tea drinkers (≥ 7 cups/week) tended to be individuals who were Asian/Pacific Islanders (23·6 %), who had the highest education level (15·6 %), with the oldest age (70–70+) (16·5 %), who had the lowest BMI (< 25) (16·6 %) and never used hormone therapy at last 2 years (16·1 %) and who did not have T2DM (15·6 %), while non-tea drinkers were more likely to be non-alcohol drinkers or past drinkers (51·4 %), heavy smokers (50·5 %), with the highest physically active (≥ 30 METs-hours/week) (49·1 %) (Table 1). Similar distributions were obtained for herbal tea intake and decaffeinated tea intake, except for hypertension and treatment status (online Supplementary Tables S1–S2); especially, individuals with treated hypertension were more commonly found in non-herbal tea drinkers (64·4 %), while women with untreated hypertension were commonly observed among non-decaffeinated tea consumers (76·9 %).

The number of person-years by main exposures of interest and incidence rates is summarised in Tables 2 and 3 and online Supplementary Table S3. Besides, results from Cox proportional hazard regression models examining associations of caffeinated tea intake with risk of NHL overall are summarised in Table 2. There were no significant associations between caffeinated tea intake and occurrence of NHL, irrespective of histologic subtype. Similar associations were observed for decaffeinated tea intake (online Supplementary Table S3). Although the increased amount of herbal tea intake was non-significantly associated with the decreased risks of NHL (hazard ratios (95 % CI) for < 1 cup per week, 1–6 cups per week and ≥ 7 cups per week: 1·19 (0·96–1·46), 1·01 (0·82, 1·24), 0·74 (0·52, 1·05); *P*-value: 0·10) after controlling for potential confounders (Table 3), there were no significant dose–response associations among women who had tea-drinking habits in current analyses (Tables 2, online Supplementary Table S3, *P*-values for trend test > 0·05), and results were similarly null for NHL subtypes. Additionally, we searched for interactions between tea-drinking habits, selected categorical variables (age group, BMI group, pack-years of smoking group, racial or ethnic group and alcohol use) and risk of NHL, no interactions were found (online Supplementary Tables S4–S8, *P*-values > 0·05). Furthermore, the results obtained by the mode imputation remained similar, and no significant changes were found between habitual tea intake and overall risks of NHL and its subtypes (*P*-value > 0·05) regardless of the amounts of tea intake and types of tea intake in the age-adjusted model and multivariable-adjusted models (data not shown). In order to minimise possible reverse causality, we performed additional analyses and excluded the first 5 years after being exposed to tea intake; however, the associations between tea-drinking habits and risk of NHL remained non-significant (data not shown).

Discussion

Overall, in a large cohort of postmenopausal women with more than 20 years of follow-up, different amounts of type-specific tea intake (caffeinated/herbal/decaffeinated tea) were not associated with the risk of NHL irrespective of histology.

Thus far, findings on the associations between the different amounts of type-specific tea intake and the risk of NHL have been inconsistent[12,13,15–19]. The inconsistencies may be partly due to the certain tea types. For example, a beneficial association of heavy green tea intake on the risk of NHL was observed in one Japanese study[16]. Green tea is especially rich in polyphenols (catechins and gallocatechin), and these compounds can induce apoptosis in lymphoma cells by inhibiting DNA replication[35,36]. However, all analyses among Western countries, such as Sweden[15] and USA[12,18], where black tea-drinking is prevalent, there were no statistically significant associations between tea

Table 1. General characteristics of study participants at year 3 according to regular tea consumed among the postmenopausal women, Women's Health Initiative Observational Study
(Numbers and percentages, *n* 62 622)

	Cups of the regular tea consumed at year 3									
	Non-drinkers (*n* 29 229)		< 1 cup per week (*n* 9908)		1–6 cups per week (*n* 13 758)		≥7 cups per week (*n* 9727)		*N* 62 622	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Socio-demographic factors										
Age at year 3										
Mean	66·3		65·8		66·4		66·7		66·3	
SD	7·3		7·3		7·3		7·2		7·3	
Age group at year 3										
50–59	6296	47·0	2315	17·3	2904	21·7	1892	14·1	13 407	
60–69	12 394	46·4	4308	16·1	5864	22·0	4131	15·5	26 697	
70–79+	10 539	46·8	3285	14·6	4990	22·2	3704	16·5	22 518	
BMI, kg/m^2										
Mean	27·0		27·2		27·2		26·4		27·0	
SD	5·7		5·8		5·7		5·4		5·7	
BMI group, kg/m^2										
< 25	12 691	46·9	4206	15·5	5677	21·0	4499	16·6	27 073	
25 to < 30	97,38	46·1	3326	15·7	4809	22·8	3261	15·4	21 134	
30 to < 35	4303	46·8	1469	16·0	2104	22·9	1315	14·3	9191	
< 35	2497	47·8	907	17·4	1168	22·4	652	12·5	5224	
Racial or ethnic group										
White (not of Hispanic origin)	24 946	46·3	8518	15·8	11 843	22·0	8619	16·0	53 926	
Black or African American	2264	56·3	664	16·5	788	19·6	306	7·6	4022	
Hispanic/Latino	1032	55·5	263	14·2	362	19·5	202	10·9	1859	
American Indian/Alaskan native	116	50·4	38	16·5	45	19·6	31	13·5	230	
Asian/Pacific Islander	569	29·5	329	17·1	574	29·8	454	23·6	1926	
Others	302	45·8	96	14·6	146	22·2	115	17·5	659	
Education level										
High school diploma/below	6319	50·8	1751	14·1	2468	19·8	1905	15·3	12 443	
School after high school	2904	49·1	859	14·5	1249	21·1	899	15·2	5911	
College degree or higher	20 006	45·2	7298	16·5	10 041	22·7	6923	15·6	44 268	
Lifestyle risk factors										
Total energy intake (kcal/d)										
Mean	1497·9		1568·8		1610·0		1622·7		1552·6	
SD	651·7		641·5		684·3		688·6		665·5	
Recreational physical activity group, METS-hours/week										
None	5404	44·8	2013	16·7	2713	22·5	19,07	15·8	12 037	
5 to < 10	4784	46·4	1604	15·6	2280	22·1	1642	15·9	10 310	
10 to < 20	7145	45·7	2463	15·8	3524	22·5	2505	16·0	15 637	
20 to < 30	3814	46·7	1273	15·6	1805	22·1	1277	15·6	8169	
≥ 30	8082	49·1	2555	15·5	3436	20·9	2396	14·6	16 469	
Pack-years of smoking group										
Non-smokers	14 930	45·2	5162	15·6	7573	22·9	5406	16·4	33 071	
< 5	4356	46·9	1491	16·0	2062	22·2	1388	14·9	9297	
5 to < 20	4240	47·3	1486	16·6	1900	21·2	1336	14·9	8962	
≥ 20	5703	50·5	1769	15·7	2223	19·7	1597	14·1	11 292	
Alcohol use										
Non-drinkers or past drinkers	9991	51·4	2615	13·5	3832	19·7	3007	15·5	19 445	
≤ 3 drinks per month	5107	42·5	2040	17·0	2963	24·6	1919	16·0	21 034	
1–4 drinks per week	9407	44·7	3572	17·0	4830	23·0	3225	15·3	12 029	
≥ 5 drinks per week	4724	46·7	1681	16·6	2133	21·1	1576	15·6	10 114	
Clinical risk factors and current medical conditions										
Hormone replacement therapy (HRT)										
Never use last 2 years	13 193	47·7	4137	15·0	5873	21·2	4443	16·1	27 646	
Oestrogen along use last 2 years	7454	46·1	2645	16·4	3635	22·5	2421	15·0	16 155	
Combined oestrogen-progestin use last 2 years	70	44·9	22	14·1	43	27·6	21	13·5	156	
Hormones use last 2 years (oestrogen or progesterone)	956	47·8	337	16·9	433	21·7	273	13·7	1999	
Both use last 2 years	7556	45·3	2767	16·6	3774	22·6	2569	15·4	16 666	
Systemic lupus erythematosus (SLE)										
Yes	155	47·7	48	14·8	58	17·8	64	19·7	325	
No	29 074	46·7	9860	15·8	13 700	22·0	9663	15·5	62 297	
Rheumatoid arthritis (RA)										
Yes	1461	48·1	464	15·3	634	20·9	476	15·7	3035	
No/other	27 768	46·6	9444	15·9	13 124	22·0	9251	15·5	59 587	

Table 1. (*Continued*)

	Cups of the regular tea consumed at year 3									
	Non-drinkers (*n* 29 229)		< 1 cup per week (*n* 9908)		1–6 cups per week (*n* 13 758)		≥7 cups per week (*n* 9727)		*N* 62 622	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Type 2 diabetes mellitus (T2DM) and treatments										
No diabetes	27 794	46·6	9492	15·9	13 095	21·9	9331	15·6	59 712	
Diabetes without treatment	416	49·3	143	16·9	173	20·5	112	13·3	844	
Diabetes with treatments	1019	49·3	273	13·2	490	23·7	284	13·8	2066	
Hypertension and treatment status										
Never hypertensive	19 881	46·5	6791	15·9	9365	21·9	6710	15·7	42 747	
Untreated hypertensive	2257	46·9	744	15·5	1023	21·3	786	16·3	4810	
Treated hypertensive	7091	47·1	2373	15·8	3370	22·4	2231	14·8	15 065	
Family history of any cancer										
Yes	18 631	46·5	6412	16·0	8824	22·0	6237	15·6	40 104	
No	10 598	47·1	3496	15·5	4934	21·9	3490	15·5	22 518	

Table 2. Associations of non-Hodgkin lymphoma (NHL) and major subtypes with regular tea intake among 62 622 postmenopausal women (Hazard ratios and 95 % confidence intervals)

	Regular tea intake (caffeinated tea, not herbal, not decaf)						
	No. of cases	Person-years	Incidence rate (per 10 000)	HR*	95 % CI	HR†	95 % CI
NHL	663						
None	315	379 987·0	8·29	1·00 (Ref.)		1·00 (Ref.)	
<1 cup per week	94	134 796·2	6·97	0·85	0·67–1·06	0·83	0·66–1·05
1–6 cups per week	141	183 940·5	7·67	0·92	0·75–1·12	0·90	0·73–1·10
≥7 cups per week	113	129 964·3	8·69	1·03	0·83–1·28	1·00	0·80–1·24
P-value				0·41‡/0·88§		0·36‡/0·65§	
Diffuse large B-cell lymphoma (DLBCL)	195						
None	83	–	2·18	1·00 (Ref.)		1·00 (Ref.)	
<1 cup per week	29	–	2·15	1·00	0·65–1·52	0·97	0·64–1·49
1–6 cups per week	46	–	2·50	1·14	0·76–1·57	1·09	0·76–1·56
≥7 cups per week	37	–	2·85	1·28	0·87–1·89	1·2	0·81–1·77
P-value				0·60‡/0. 20§		0·78‡/0·35§	
Follicular lymphoma (FL)	128						
None	68	–	1·79	1·00 (Ref.)		1·00 (Ref.)	
<1 cup per week	12	–	0·89	0·50	0·27–0·92	0·49	0·27–0·91
1–6 cups per week	28	–	1·52	0·85	0·55–1·32	0·84	0·54–1·31
≥7 cups per week	20	–	1·54	0·85	0·52–1·40	0·86	0·52–1·42
P-value				0·17‡/0·42§		0·16‡/0·44§	
Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)	51						
None	24	–	0·63	1·00 (Ref.)		1·00 (Ref.)	
<1 cup per week	10	–	0·74	1·18	0·56–2·46	1·17	0·56–2·45
1–6 cups per week	13	–	0·71	1·12	0·57–2·19	1·10	0·56–2·17
≥7 cups per week	4	–	0·31	0·49	0·17–1·40	0·47	0·16–1·34
P-value				0·47‡/0·39§		0·44‡/0·34§	

* Model adjusted for age group (50–59, 60–69 and 70–79+) only.
† Model adjusted for all socio-demographic risk factors, lifestyle risk factors, clinical risk factors and current medical conditions.
‡ *P-value* was estimated from Cox proportional hazard model across the total amount of regular tea consumed (categorical variable) at year 3.
§ *P-value* was estimated from linear trend test.

intake and risk of NHL. Existing evidence suggests that green teas have a higher concentration of antioxidants than black tea because they are the least processed tea with slight natural oxidation[37]. Additionally, antioxidant properties in decaffeinated tea have been reduced during decaffeination[38]. Thus, the differences in types of tea intake are likely to account for inconsistent associations. However, we could not adjust for the specific formation process due to a lack of information on whether those teas are green tea or black tea in the current study. Besides, the study which was conducted in Japan indicated that participants who had heavy tea consumptions (≥ 5 cups/d) had a significantly decreased risk of NHL. In contrast, among this population, the overall tea intake level is relatively low compared with the Japanese study[16].

The inconsistencies in findings across studies might also be due to differences in exposure assessment; for example, the definition of tea intake (current *v.* non-current or ever *v.* never or cumulative lifetime intake) and differences in the distribution of NHL subtypes could also contribute to inconsistency. Moreover, lacking information about tea preparation methods

Table 3. Associations of non-Hodgkin lymphoma (NHL) and major subtypes with herbal tea intake among 62 622 postmenopausal women (Hazard ratios and 95 % confidence intervals)

	Herbal tea intake						
	No. of cases	Person-years	Incidence rate (per 10 000)	HR*	95 % CI	HR†	95 % CI
NHL	663						
None	388	482 929·8	8·03	1·00 (Ref.)		1·00 (Ref.)	
Cup per week	119	130 765·4	9·10	1. 18	0·96–1·45	1·19	0·96–1·46
1–6 cups per week	123	156 933·8	7·84	1·01	0·83–1·24	1·01	0·82–1·24
≥7 cups per week	33	58 059·0	5·69	0·73	0·51–1·05	0·74	0·52–1·05
P-value				0·10‡/0·42§		0·10‡/0·43§	
Diffuse large B-cell lymphoma (DLBCL)	195						
None	115	–	2·38	1·00 (Ref.)		1·00 (Ref.)	
<1 cup per week	32	–	2·45	1·09	0·73–1·61	1·07	0·72–1·59
1–6 cups per week	38	–	2·42	1·07	0·74–1·54	1·03	0·71–1·49
≥7 cups per week	10	–	1·72	0·76	0·40–1·44	0·73	0·38–1·40
P-value				0·77‡/0·79§		0·76‡/0·21§	
Follicular lymphoma (FL)	128			–		–	
None	83	–	1·72	1·00 (Ref.)		1·00 (Ref.)	
<1 cup per week	18	–	1·38	0·82	0·49–1·37	0·80	0·48–1·34
1–6 cups per week	19	–	1·21	0·72	0·44–1·18	0·71	0·43–1·18
≥7 cups per week	8	–	1·38	0·82	0·40–1·69	0·83	0·40–1·73
P-value				0·56‡/0·20§		0·54‡/0·16§	
Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)	51						
Non-drinkers	28	482 929·8	0·58	1·00 (Ref.)		1·00 (Ref.)	
Drinkers	23	345 758·2	0·67	1·16	0·66–2·01	1·11	0·63–1·95
P-value				0·61‡		0·72‡	

* Model adjusted for age group (50–59, 60–69 and 70–79+) only.
† Model adjusted for all socio-demographic risk factors, lifestyle risk factors, clinical risk factors and current medical conditions.
‡ *P*-value was estimated from Cox proportional hazard model across the total amount of herbal tea consumed (categorical variable) at year 3.
§ *P*-value was estimated from linear trend test.

might lead to inconsistencies. In particular, studies indicate that amounts of epigallocatechin gallate are almost equal in the first two cups brewed, but it can be largely declined in the third cup[39]. However, the relevant information was not asked for in the WHI[35,36].

Additionally, some clinical studies indicate that many drug interactions are caused by Camellia sinensis since its constituents can interact with the cytochrome P450 system[40], which can be related to drug metabolism and occurrence of NHL. Although hypertension treatments, T2DM treatments and hormone therapy were adjusted in the multivariable-adjusted analyses, postmenopausal women may take many other medications, and we had limited power to examine each specific medication for the current study.

As mentioned previously, although herbal tea is called tea, it is quite different from traditional tea. This type of tea contains the major bioactive compounds known as monomeric flavonoids, such as anthocyanin, biochanin A, carotenoids, coumarins, curcumins, ellagic acid, plant sterols and terpenoids, which may protect against several chronic diseases[41]. In accordance with the existing evidence, we observed that the risk of NHL decreased with an increase in the cups of herbal tea intake, albeit the inverse dose–response association was not statistically significant. Our findings were probably due to the fact that women who had habitual herbal tea intake might be more health conscious and would be more likely to choose a healthy lifestyle. This hypothesis was likely true and could be confirmed by examining the distribution of several health-related lifestyle factors[42], such as BMI, physical activities, smoking status and alcohol status according to herbal tea consumption (online Supplementary Table S9). Although previous case–control studies reported a significant inverse association between herbal tea intake and solid cancer risk[43], further research is needed to evaluate the association between specific herbal teas and risks of NHL and certain subtypes of NHL.

The major strength of our study is the use of the prospective study design with a relatively large number of NHL cases ascertained over a long follow-up period, and only about 4 % of self-reported NHL cases did not get adjudicated because of not being able to get their medical records[44]. This study had rich data on a wide range of potential confounders; besides, in order to avoid potential residual confounders, continuous variables, such as age, BMI and pack-years of smoking, had been used to replace categorical age, BMI and smoking status in multivariable-adjusted models, although results remained similar. In addition, important interactions between tea-drinking habits and covariates, such as smoking history, alcohol consumption, racial or ethnic group, BMI and age, were examined. To reduce bias, the imputation method was further conducted in this work, and categorical missing data were replaced by mode after applying standard complete-case analysis to the filled-in data, although no significant associations were found. Moreover, we further conducted lag analyses and excluded the first 5 years of follow-up after the habitual tea intake record to minimise reverse causality bias.

However, there are some limitations and pitfalls, which should be considered. First, our findings for tea intake should be interpreted with caution because information on tea intake

was self-reported and could not be validated since it was not captured on the diet assessment tools. Thus, potential recall bias may be present in this study. However, observational epidemiological study of tea intake usually relies on self-reported exposure data since there is no other practical way of assessing tea intake at present. In addition, we only assessed tea information at year 3 of follow-up and did not examine changes in tea-drinking habits (caffeinated/decaffeinated tea were available), whereas the risk of NHL is expected to associate with cumulative tea intake over one's lifetime rather than a 3-month window. As a control measure, we compared the tea intake at year 3 with year 6 and year 8 in the WHI-OS cohort. The patterns and distributions of tea intake remained similar between these time points. Therefore, we have some confidence that the tea-drinking habits among women in WHI-OS remained stable over time. Information on whether participants drank traditional tea products or tea beverages (i.e. iced tea, sweet tea, etc.) or certain types of tea (i.e. black, green or other types of non-herbal teas) was not available. Since men and younger women were not included in the current study, we could not examine sex differences, so our findings may not be generalised to other populations.

In conclusion, the results from our study indicate that habitual tea intake at the current consumption level was not associated with risk of NHL in the US postmenopausal women. More epidemiological studies, which include detailed assessments on the types of tea or tea preparation methods, are needed to further explore the associations between tea-drinking habits and the risk of NHL.

Acknowledgements

This work was supported by Women's Health Initiative. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C and HHSN268201600004C. We thank the following WHI investigators for their expertise and help. Program Office: (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, Nancy Geller. Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet L. Anderson, Ross Prentice, Charles Kooperberg, Lisa Johnson, Andrea LaCroix, Lesley Tinker, Marian Neuhouser, Susan Heckbert, Alex Reiner, Chongzhi Di, Xiaoling Song, Wayne Rosamond, Shirley Beresford, Chu Chen, Barbara Cochrane. Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson, Shari Bassuk, Howard Sesso, Lu Wang; (MedStar Health Research Institute, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia Stefanick, Mark Hlatky, Marco Perez, Themistocles (Tim) Assimes and Jean Tang; (The Ohio State University, Columbus, OH) Rebecca Jackson, Randall Harris, Electra Paskett, W. Jerry Mysiw, Michael Blumenfeld; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson, Tamsen Bassford, Cheryl Ritenbaugh, Zhao Chen, Marcia Ko; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende, Michael LaMonte, Amy Millen, Heather Ochs-Balcom, Christopher Andrews; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher, Michael Perri, Andrew Kaunitz, R. Stan Williams, Yvonne Brinson; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson, Robert Wallace, James Torner, Susan Johnson, Linda Snetselaar; (University of Nevada, Reno, NV) Robert Brunner, Sandra Daugherty1; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller, Jane Cauley, N. Carole Milas; (Wake Forest University School of Medicine, WinstonSalem, NC) Sally Shumaker, Stephen Rapp, Claudine Legault, Mark Espeland, Laura Coker, Michelle Naughton. Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland, Sally Shumaker, Stephen Rapp, Claudine Legault, Laura Coker, Michelle Naughton. All participants signed informed consent. The original protocol was approved by all forty institutional review boards (IRB) and was obtained from each of the participating WHI sites and from the Fred Hutchinson Cancer Research Center, which currently serves as the IRB of record for the WHI. Federalwide assurance number is 00001920, and the registration numbers for each of the IRBs are as follows: Fred Hutchinson Cancer Research Center IRB registration no. Com A (00000021), Com B (00000022), Com C (00005619), Com D (00009831).

There is no funding to disclose.

The authors' responsibilities were as follows: Z. W., J. L. and Z. C. substantially designed the research; Z. K. W., J. H. L. and Z.X.C. acquired the data and performed the analyses; Z. W., J. L. and Z. C. participated in the interpretation of the results; Z. W., J. L. and Z. C. drafted the manuscript; all authors made critical revisions to the manuscript for intellectual content; J. L. and Z. C. supervised all aspects of the conduct of the study. All authors read and approved the final manuscript.

The authors declare that there is no conflict of interest.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114522000447

References

1. Society AC (2021) Cancer Facts & Figures 2021. American Cancer Society. https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/key-statistics.html#references (accessed February 2021).
2. Groves FD, Linet MS, Travis LB, *et al.* (2000) Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. *J Natl Cancer Inst* **92**, 1240–1251.
3. Van de Schans SAM, Issa DE, Visser O, *et al.* (2012) Diverging trends in incidence and mortality, and improved survival of non-Hodgkin's lymphoma, in the Netherlands, 1989–2007. *Ann Oncol* **23**, 171–182.
4. Ries LA, Harkins D, Krapcho M, *et al.* (2006) SEER Cancer Statistics Review, 1975–2003. Bethesda, MD: National Cancer Institute. https://seer.cancer.gov/csr/1975_2003/ (accessed November 2005).

5. Miranda-Filho A, Pineros M, Znaor A, *et al.* (2019) Global patterns and trends in the incidence of non-Hodgkin lymphoma. *Cancer Causes Control* **30**, 489–499.
6. Ekstrom-Smedby K (2006) Epidemiology and etiology of non-Hodgkin lymphoma – a review. *Acta Oncol* **45**, 258–271.
7. Hu S, Zhou D, Wu Y, *et al.* (2019) Autoimmune disease-associated non-Hodgkin's lymphoma-a large retrospective study from China. *Ann Hematol* **98**, 445–455.
8. Herrinton LJ & Friedman GD (1998) Cigarette smoking and risk of non-Hodgkin's lymphoma subtypes. *Cancer Epidemiol Prev Biomarker* **7**, 25–28.
9. Chiu BC, Cerhan JR, Gapstur SM, *et al.* (1999) Alcohol consumption and non-Hodgkin lymphoma in a cohort of older women. *Br J Cancer* **80**, 1476–1482.
10. Hoffman-Goetz L & Pedersen BK (1994) Exercise and the immune system: a model of the stress response? *Immunol Today* **15**, 382–387.
11. Butt MS, Imran A, Sharif MK, *et al.* (2014) Black tea polyphenols: a mechanistic treatise. *Crit Rev Food Sci Nutr* **54**, 1002–1011.
12. Chiu BC, Dave BJ, Ward MH, *et al.* (2008) Dietary factors and risk of t(14;18)-defined subgroups of non-Hodgkin lymphoma. *Cancer Causes Control* **19**, 859–867.
13. Zheng W, Doyle TJ, Kushi LH, *et al.* (1996) Tea consumption and cancer incidence in a prospective cohort study of postmenopausal women. *Am J Epidemiol* **144**, 175–182.
14. Sun CL, Yuan JM, Koh WP, *et al.* (2006) Green tea, black tea and colorectal cancer risk: a meta-analysis of epidemiologic studies. *Carcinog* **27**, 1301–1309.
15. Chang ET, Smedby KE, Zhang SM, *et al.* (2005) Dietary factors and risk of non-Hodgkin lymphoma in men and women. *Cancer Epidemiol Biomarkers Prev* **14**, 512–520.
16. Naganuma T, Kuriyama S, Kakizaki M, *et al.* (2009) Green tea consumption and hematologic malignancies in Japan: the Ohsaki study. *Am J Epidemiol* **170**, 730–738.
17. Ugai T, Matsuo K, Sawada N, *et al.* (2017) Coffee and green tea consumption and subsequent risk of malignant lymphoma and multiple myeloma in Japan: the Japan Public Health Center-based Prospective Study. *Cancer Epidemiol Biomarkers Prev* **26**, 1352–1356.
18. Ward MH, Zahm SH, Weisenburger DD, *et al.* (1994) Dietary factors and non-Hodgkin's lymphoma in Nebraska (United States). *Cancer Causes Control* **5**, 422–432.
19. Parodi S, Santi I, Marani E, *et al.* (2016) Lifestyle factors and risk of leukemia and non-Hodgkin's lymphoma: a case-control study. *Cancer Causes Control* **27**, 367–375.
20. Bertolini F, Fusetti L, Rabascio C, *et al.* (2000) Inhibition of angiogenesis and induction of endothelial and tumor cell apoptosis by green tea in animal models of human high-grade non-Hodgkin's lymphoma. *Leukemia* **14**, 1477–1482.
21. Lee YK, Bone ND, Strege AK, *et al.* (2004) VEGF receptor phosphorylation status and apoptosis is modulated by a green tea component, epigallocatechin-3-gallate (EGCG), in B-cell chronic lymphocytic leukemia. *Blood* **104**, 788–794.
22. Kondo T, Ohta T, Igura K, *et al.* (2002) Tea catechins inhibit angiogenesis *in vitro*, measured by human endothelial cell growth, migration and tube formation, through inhibition of VEGF receptor binding. *Cancer Lett* **180**, 139–144.
23. Jabir NR, Islam MT, Tabrez S, *et al.* (2018) An insight towards anticancer potential of major coffee constituents. *BioFactors* **44**, 315–326.
24. Franceschi S, Serraino D, Carbone A, *et al.* (1989) Dietary factors and non-Hodgkin's lymphoma: a case-control study in the northeastern part of Italy. *Nutr Cancer* **12**, 333–341.
25. Lallement G & Bezanger B (1970) Flavonoides de quelques labiate medicinales (rosmarin, menthe, sauge)(The flavonoid content of some medical plants from the labiatae family (rosemary, peppermint, sage)). *Plant Med Phytother* **4**, 92–107.
26. Green CJ, de Dauwe P, Boyle T, *et al.* (2014) Tea, coffee, and milk consumption and colorectal cancer risk. *J Epidemiol* **24**, 146–153.
27. Nations FAOU (2016) Food and Agriculture Organization of the United Nations Statistics Division. http://faostat3.fao.org/home/index.html (accessed May 2021).
28. Banerjee S, Maity P, Mukherjee S, *et al.* (2007) Black tea prevents cigarette smoke-induced apoptosis and lung damage. *J Inflamm* **4**, 3.
29. Schwarz B, Bischof HP & Kunze M (1994) Coffee, tea, and lifestyle. *Prev Med* **23**, 377–384.
30. Kao YH, Chang HH, Lee MJ, *et al.* (2006) Tea, obesity, and diabetes. *Mol Nutr Food Res* **50**, 188–210.
31. Study TWHI (1998) Design of the women's health initiative clinical trial and observational study. *Controlled Clin Trial* **19**, 61–109.
32. Langer RD, White E, Lewis CE, *et al.* (2003) The women's health initiative observational study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol* **13**, S107–121.
33. Curb JD, McTiernan A, Heckbert SR, *et al.* (2003) Outcomes ascertainment and adjudication methods in the women's health initiative. *Ann Epidemiol* **13**, S122–128.
34. Batista GE & Monard MC (2003) An analysis of four missing data treatment methods for supervised learning. *Appl Artif Intell* **17**, 519–533.
35. Fang MZ, Wang Y, Ai N, *et al.* (2003) Tea polyphenol (-)-epigallocatechin-3-gallate inhibits DNA methyltransferase and reactivates methylation-silenced genes in cancer cell lines. *Cancer Res* **63**, 7563–7570.
36. Siddiqui IA, Adhami VM, Bharali DJ, *et al.* (2009) Introducing nanochemoprevention as a novel approach for cancer control: proof of principle with green tea polyphenol epigallocatechin-3-gallate. *Cancer Res* **69**, 1712–1716.
37. Lee KW, Lee HJ & Lee CY (2002) Antioxidant activity of black tea *v.* green tea. *J Nutr* **132**, 785.
38. Sang S, Lambert JD, Ho CT, *et al.* (2011) The chemistry and biotransformation of tea constituents. *Pharmacol Res* **64**, 87–99.
39. Wiseman S, Mulder T & Rietveld A (2001) Tea flavonoids: bioavailability *in vivo* and effects on cell signaling pathways *in vitro*. *Antioxidants Redox Signaling* **3**, 1009–1021.
40. Albassam AA & Markowitz JS (2017) An appraisal of drug-drug interactions with green tea (Camellia sinensis). *Planta Med* **83**, 496–508.
41. Craig WJ (1999) Health-promoting properties of common herbs. *Am J Clin Nutr* **70**, 491S–499S.
42. Simard JF, Baecklund F, Chang ET, *et al.* (2013) Lifestyle factors, autoimmune disease and family history in prognosis of non-hodgkin lymphoma overall and subtypes. *Int J Cancer* **132**, 2659–2666.
43. Riza E, Linos A, Petralias A, *et al.* (2015) The effect of Greek herbal tea consumption on thyroid cancer: a case-control study. *Eur J Public Health* **25**, 1001–1005.
44. Women's Health Initiative 2019 (2021) Annual Progress Report. Women's Health Initiative 2019 Annual Progress Report. https://www.whi.org/doc/2019-Annual.pdf (accessed October 2021).