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Dietary Intakes and Risk of Lymphoid and Myeloid Leukemia in the European Prospective Investigation into Cancer and Nutrition (EPIC)

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The etiology of leukemias cannot entirely be explained by known risk factors, including ionizing radiation, benzene exposure, and infection with human T cell leukemia virus. A number of studies suggested that diet influences the risk of adult leukemias. However, results have been largely inconsistent. We examined the potential association between dietary factors and risk of leukemias among participants of the European Prospective Investigation into Cancer and Nutrition study. Among the 477,325 participants with mean follow-up of 11.34 yr (SD = 2.47), 773 leukemias (373 and 342 cases of lymphoid and myeloid leukemia, respectively) were identified. Diet over the previous 12 mo was assessed at baseline

using a validated country-specific dietary questionnaire. Cox proportional hazards regression was used to explore the association between dietary factors that have previously been associated with leukemia risk, including red and processed meat, poultry, offal, fish, dairy products, vegetables, fruits, and seeds/nuts, and risk of both lymphoid and myeloid leukemias. No significant associations were observed between dietary measures and total, lymphoid, and myeloid leukemias. Additional subtype analyses showed no dietary association with risk of major subtypes of leukemias. In summary, this study did not support a possible link between selected dietary factors and risk of leukemias.

INTRODUCTION

In 1997, the World Cancer Research Fund and the American Institute for Cancer Research estimated that 30–40% of all cancers could be prevented by modifying lifestyle factors like diet and exercise (1). Several animal and epidemiological studies support the possible association between dietary factors and risk of cancer including colon, pancreas, breast, stomach, esophageal, bladder, lung, and oral cancer (2,3). Although a number of epidemiological studies have suggested that intake of meat, fruit, and vegetables and dairy products influences risk of hematopoietic cancers including leukemias, results have been inconclusive (2).

Previous studies have suggested that increased intake of fish, fruit, and vegetables is associated with a lower risk of leukemias and/or leukemia subtypes (4–9), whereas high intake of red and processed meat may play a role in leukemia development (7,10,11). In contrast, other studies either showed no dietary association with risk of lymphoid and myeloid leukemias (12) or showed contradictory effects (i.e., for milk consumption) (4, 7). Vegetables and fruits contain many potentially protective substances, including several antioxidants, as well as phytochemicals with antiproliferative capabilities. They are also a rich source of folic acid, which plays an important role in the synthesis, repair, and methylation of DNA (1). There are no well-established mechanisms by which milk and dairy products could affect hematopoietic cancers. Dietary calcium might protect from cancer through reducing proliferation and inducing differentiation (13,14). On the other hand, calcium may restrict the bioavailability of vitamin D, which promotes differentiation and apoptosis and inhibits cancer cell growth in experimental studies. It has also been hypothesized that bovine leukemia virus might transmit through milk to humans, although there is no direct evidence for this (1). Nuts and seeds are nutrient dense and provide protein, unsaturated fatty acids, dietary fiber, and many bioactive constituents, such as tocopherols, phytosterols, folic acid, selenium, and magnesium, which are purported to have antioxidant, antiinflammatory, or anticarcinogenetic properties, a reason why a protective effect of nut consumption on cancer risk might be hypothesized (15).

In the present study we examined the potential association between risk of leukemias and intake of total vegetables, total fruits, total nuts/seeds, total dairy products, red meat, processed meat, poultry, offal, and fish (Supplemental Online Resource 1) in the European Prospective Investigation into Cancer and Nutrition (EPIC). As classification of leukemias has changed in recent years, with the lymphoid leukemias now grouped with lymphomas (16,17), we present the results for the old definition of leukemias, including myeloid and lymphoid leukemias, and separately for both leukemias as to retain comparison with previously published reports. We also explored risk by major leukemia subgroups [i.e., acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and chronic lymphoid leukemia (CLL)]. The results on CLL are updated analyses, with 4 additional years of follow-up, of a previous report in which we reported on an increased risk of CLL associated with a higher meat and dairy consumption (18).

MATERIAL AND METHODS

Study Population

EPIC is a large prospective cohort with about half a million individuals from 10 European countries (Denmark, France, Greece, Germany, Italy, Netherlands, Norway, Spain, Sweden, and United Kingdom) that was set up to examine associations between cancer risk and nutrition and metabolic risk factors. Details of the study design have been described elsewhere (19,20). Briefly, recruitment of subjects took place between 1992 and 2000 and included participants of both genders, mostly in the age range 35–70 at recruitment. After providing informed consent, standardized lifestyle and personal history questionnaires and anthropometric data were collected from most participants. In addition, diet over the previous 12 mo was measured at recruitment by validated country-specific questionnaires designed to ensure high compliance and better measures of local dietary habits (19,20). The EPIC study was approved by the review board of the International Agency for Research on Cancer and by all local institutes recruiting participants.

Participants were excluded if they did not complete either the diet and/or lifestyle questionnaire ($n = 6{,}253$), or if they were in the upper or lower 1% of the ratio of energy intake to estimated energy requirement ($n = 9{,}601$). Prevalent cancer cases of other sites and previous leukemia were excluded from the study. The final analytic cohort comprised 142,259 men and 335,066 women.

Outcome Assessment

Incident primary leukemia cancers were identified by either population cancer registries (Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) or other methods, such as health insurance records, pathology registries, and active contact of study subjects or next of kin (France, Germany, and Greece). The diagnosis, tumor site classification, and morphology of each case were based on *International Classification of Diseases for Oncology*, 2nd edition (ICD-O-2) which was reclassified according to the recently published ICD-O-3 (Supplemental Online Resource 2). The follow-up period for the present study was for data reports received at International Agency for Research on Cancer to the end of 2010. Follow-up time was accrued up to the date of last known contact, the diagnosis date, or the date of death, whichever came first. The present analysis included 773 myeloid and lymphoid leukemia cases (386 males and 387 females) and 476,552 noncases (141,873 males and 334,679 females).

Dietary Measurements

Diet over the previous 12 mo was assessed using country-specific dietary assessment methods that were developed based on a common core protocol (20). Centers in France, Greece, Germany, Italy, the Netherlands, and Spain estimated individual average portions systematically by extensive self-administered quantitative dietary questionnaires, whereas semiquantitative food-frequency questionnaires with the same standard portions were assigned to all subjects in Denmark, United Kingdom, Norway, and Umea. A combination of methods was used to estimate portion size in Malmo. All dietary questionnaires have been validated previously within each country (21). In addition to the baseline dietary questionnaire, standardized computer-based 24-h dietary recall measurements were collected from an 8% random sample of the study population with the aim to calibrate measurements and improve the comparability of dietary data across the participating centers (22, 23).

Statistical Analyses

All statistical analyses were conducted using Statistical Analysis Software, version 9.2 (SAS Institute, Cary, NC). Multivariable Cox regression models were used to estimate leukemia hazard ratios (HRs) and 95% confidence intervals (CI) using the PHREG procedure. Age was used as the underlying time variable, with entry time defined as the subject's age at recruitment, and exit time defined as the subject's age at diagnosis of leukemia (all types), death, loss to follow-up or censoring date at the end of follow-up period, whichever came first. Models were stratified by study center, sex, and age at recruitment (1-yr categories). To improve comparability of data across study centers and to partially correct the relative risk estimates for the measurement error of dietary intakes, a fixed effect linear regression calibration model was used utilizing the 24-h dietary recall data taken at baseline from a subset of the cohort ($n = 34{,}436$) as described previously (24). The 24-h dietary recall data were regressed on dietary questionnaire values, with adjustment for the same list of covariates as included in the risk analysis, and further control for the week day and season of recall measurements. Country- and sex-specific calibration models were used to obtain individual calibrated values of dietary exposure for all participants (24). Models were fitted with continuous dietary variables separately for calibrated and uncalibrated measurements, and for categorized uncalibrated variables in quintiles (or quartiles for nut/seed intake) based on the frequency distribution of the whole study population. The standard error of the deattenuated coefficients was corrected through bootstrap sampling. Tests of linear trend across categories were conducted by fitting a model treating the quintile or quartile categories as a continuous variable. Regression models were adjusted for physical activity (sex-specific quartiles of combined recreational, household, and occupational physical activity; categorical), education (indicator of socioeconomic status; categorical), smoking status (never, former smoker, current smoker), alcohol intake [never, former drinker, current drinker (at recruitment), and past and current drinker], body mass index (BMI; categorical, sex specific quartiles), and total energy intake (continuous, kcal/day). Moreover, multivariate analyses on dietary intake variables were further mutually adjusted for each other. Statistical significance of the interactions with sex, smoking status, BMI, and alcohol intake on a multiplicative scale was assessed by likelihood ratio tests with a cross-product term. Analyses were stratified by lymphoid versus myeloid leukemias and subtypes of AML, CML, and CLL. Because of the relatively modest number of cases, quartiles instead of quintiles were used in these subtype analyses. In addition, analyses were repeated after excluding cases diagnosed in the first 2 yr of follow-up to remove the possibility that underlying diseases would influence dietary habits.

RESULTS

After an average of 11.34 yr follow-up (SD = 2.47 yr; 5,414,491 person-yr in total), there were 773 leukemia cases including 342 myeloid leukemias, 373 lymphoid leukemias, 29 leukemia not otherwise specified, and 29 other specified leukemias among the 477,325 participants. The most common subtypes of myeloid and lymphoid leukemia were AML ($n = 187$), CML ($n = 80$), acute monocytic leukemia ($n = 12$), acute myelomonocytic leukemia ($n = 18$), chronic myelomonocytic leukemia ($n = 25$) and CLL ($n = 333$) and acute lymphoid leukemia (ALL) (n = 21), respectively. The numbers of participants, person-yr of follow-up and numbers of leukemia cases according to sex and country are shown in Table 1. The baseline characteristics of the participants in the whole cohort, as well as in the top and bottom quintiles of the dietary variables are shown in Tables 2 and 3. A higher proportion of women was never smokers compared with men. Age, BMI, and energy intake of both men and women were in general highest in the highest quintile of all intake variables. The majority of men in the highest quintile of meat intake were smoker or former smoker with low education but high physical activity level.

Table 4 shows the association between dietary intake variables and risk of total leukemias and leukemia subtypes. No significant association was seen between total, myeloid, and lymphoid leukemias and examined dietary intakes. The results of leukemia subtype analyses (Table 5) showed no significant association with dietary intake as well. Results did not notably change when excluding cases diagnosed in first 2 yr of follow-up ($n = 106$) or when dietary intake variables were mutually adjusted for each other (data not shown).

TABLE 1
Baseline characteristics of participants by country in the European Prospective Investigation into Cancer and Nutrition study, follow-up 1992–2010

Country	Number		Follow-up time (yr)		Person-yr		Number of leukemia cases		Age at recruitment	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
France		67,386		10.45		704,152		2		52.72
Italy	14,029	30,512	11.65	11.56	163,406	352,605	30	40	50.18	50.64
Spain	15,148	24,854	12.38	12.31	187,490	305,985	34	27	50.70	48.32
UK	22,853	52,544	11.40	11.50	260,561	604,110	56	81	52.94	47.65
The Netherlands	9,639	26,866	12.18	12.15	117,427	326,319	11	44	43.20	51.02
Greece	10,807	15,225	9.29	9.90	100,448	150,765	15	13	52.79	53.31
Germany	21,172	27,411	10.19	10.21	215,733	279,900	64	23	52.45	49.12
Sweden	22,317	26,376	13.60	13.88	303,544	366,156	78	63	51.90	52.02
Denmark	26,294	28,722	11.20	11.51	294,419	330,469	98	59	56.61	56.75
Norway		35,170		9.98		351,003		35		48.10
Overall	142,259	335,066	11.5	11.3	1,643,027	3,771,463	386	387	52.2	50.8

DISCUSSION

Consumption of red and processed meat, poultry, offal, fish, fruit, nuts, and vegetable were not associated with risk of lymphoid and myeloid leukemias in this prospective cohort of the European population. This study has several strengths, including a wide range of dietary and lifestyle habits as well as the large size of the cohort that enabled us to investigate most major leukemia subtypes. Moreover, we used a calibration approach to adjust for the systematic and random intraindividual and intercenter errors to increase the validity of the dietary exposure assessments (21–24).

Our study did not show a significant association between major food groups and total leukemias. Results from some case control studies have suggested that increased risk of leukemias is associated with higher consumption of processed meat (10, 11). However, consistent with our results, 2 prospective cohort studies have shown no association between meat intake and leukemia risk (5, 25). A population-based case-control study in Canada showed that higher intake of fresh fish was associated with lower risk of leukemias (6). Consistent with our study, Ross et al. (5) did not show any significant association between fish intake and risk of total leukemia and subtypes.

In a case-control study, Kasim et al. (12) showed no association between vegetables and fruit intake and leukemia risk, whereas the Iowa women's health study suggested a reduction in risk of leukemias with higher intake of vegetables (5). Folic acid is high in many vegetables, in particular leafy vegetables (26). Some studies have suggested that deviations in folic acid metabolism either through folic acid deficiency or polymorphic variation may play a key role in the cause of leukemias, in particular ALL (27, 28). In our study we did not observe an association between vegetable and fruit intake and leukemia risk. Numbers of ALL were unfortunately prohibitively low to perform meaningful analyses. Use of different dietary questionnaire and food grouping as well as different study design and populations and age distribution might explain some of the discrepancies in the published results.

Lymphoid Leukemias

We previously published on the association between non-Hodgkin lymphoma/subtypes and meat and dairy intake within the EPIC cohort (18). A significant increased risk of CLL for higher intake of processed meat (HR = 1.75, 95% CI: 1.11, 2.75) and poultry (HR = 2.60, 95% CI: 1.56, 4.36) was reported. The results of this extended follow-up of the EPIC cohort, including 100 additional CLL cases, did not confirm these previous findings. As such it seems that CLL is not related to processed meat or poultry intake. This is in agreement with findings of two other prospective cohorts which showed no association between risk of CLL and processed meat intake (case number CLL/small lymphocytic leukemia = 1,129 and CLL = 58, respectively) (5,29).

Myeloid Leukemias

Our study showed no significant association between dietary factors and myeloid leukemias or its subtypes. A recent prospective cohort study, with a larger number of AML cases than our study (338 vs. 187) found no association between AML and processed meat intake (30). Similarly, the Iowa women's health study (case number = 48) showed no association between AML and meat and vegetables intake (5).

Several potential limitations should be considered when interpreting our study findings. First, systematic and random errors may still be present in the 24-h dietary recall that could affect the validity of the data calibration. Moreover, we assessed dietary intake only at baseline, given the long follow-up, entailing

TABLE 2

Baseline characteristics of male participants by lowest and highest intake (g/day) categories of red meat, processed meat, poultry, fish, fruits, vegetables, and nuts and seeds, EPIC study, follow-up 1992–2010

		Red meat		Processed meat		Poultry		Fish	
Characteristic	Total cohort	1thQ (0–12.1)	5thQ (70.4–722.2)	1thQ (0–7.4)	5thQ (50–770.8)	1thQ (0–3.4)	5thQ (31.4–690)	1thQ (0–6.2)	5thQ (45.2–755.6)
Age at recruitment, yr[a]	52.2 (10.1)	49.0 (12.2)	52.5 (9.1)	50.8 (13.1)	51.8 (9.2)	50.8 (12.1)	52.7 (9.4)	47.9 (11.8)	53.8 (8.5)
BMI at baseline [a,b]	26.5 (3.7)	25.2 (3.6)	26.9 (3.7)	26.2 (3.9)	26.8 (3.6)	25.5 (3.6)	27.2 (3.6)	25.6 (3.7)	27.3 (3.7)
Total energy intake (kcal/day)[a]	2,410 (662)	2,081 (631)	2,683 (641)	2,178 (618)	2,697 (677)	2,268 (664)	2,581 (678)	2,274 (669)	2,634 (668)
Alcohol intake (%)									
Never	1.2	1.1	0.9	2.7	0.7	0.8	1.8	0.7	1.7
Former drinker	3.3	3.3	2.4	4.8	3.0	2.0	5.1	1.9	5.4
Current drinker	2.9	7.1	1.8	9.6	0.8	5.0	3.1	3.5	2.5
Past and current drinker	69.2	58.7	76.3	75.4	66.9	48.6	81.3	40.3	81.4
Not specified	23.4	29.8	18.6	7.5	28.7	43.6	8.8	53.6	9.0
Smoking habits (%)									
Never	33.0	45.9	26.4	36.8	30.4	38.7	30.6	40.2	29.0
Former smoker	36.3	34.4	34.4	34.1	36.3	35.0	37.7	32.7	36.7
Current smoker	29.4	18.4	38.3	26.3	32.6	25.5	29.9	26.3	33.3
Not specified	1.4	1.3	1.0	2.8	0.7	0.8	1.8	0.8	1.0
Education (%)									
None	4.1	3.3	3.5	7.9	3.7	1.3	8.6	1.2	10.2
Primary school	29.9	18.5	33.4	25.8	33.6	26.5	33.6	23.7	33.4
Technical/professional school	24.3	20.6	27.5	17.3	25.9	22.0	22.4	27.2	20.6
Secondary school	13.1	14.6	11.9	12.3	11.1	14.0	11.8	17.3	10.6
University degree	26.7	38.0	22.1	32.9	25.0	33.0	21.7	28.6	23.5
Not specified	1.8	5.1	0.7	3.8	0.7	3.3	1.8	2.1	1.7
Physical activity (%)									
Low	18.4	14.9	20.6	18.5	16.5	17.0	20.0	14.0	20.3
Medium	26.2	23.6	25.9	31.0	25.5	27.8	28.7	22.4	28.6
High	32.6	29.0	34.0	37.2	33.9	31.1	34.9	27.8	35.2
Very high	12.2	9.8	15.8	11.3	13.9	9.6	14.1	10.7	14.8
Not specified	10.6	22.7	3.8	2.0	10.3	14.5	2.3	25.2	1.2

(Continued on next page)

TABLE 2
Baseline characteristics of male participants by lowest and highest intake (g/day) categories of red meat, processed meat, poultry, fish, fruits, vegetables and nuts and seeds, EPIC study, follow-up 1992–2010 *(Continued)*

	Nuts and seeds		Fruit		Vegetables		Dairy products	
	1thQ (0)	5thQ (5.34–286.1)	1thQ (0–91.1)	5thQ (346.6–4646.8)	1thQ (0–97.8)	5thQ (307–2979.3)	1thQ (0–134.1)	5thQ (490.2–4566.1)
Age at recruitment, yr[a]	51.3 (10.0)	52.5 (11.3)	51.4 (10.0)	52.0 (10.0)	51.3 (10.0)	52.5 (11.3)	52.1 (9.2)	51.9 (11.2)
BMI at baseline[a,b]	26. 3 (3.6)	27.2 (3.9)	26.2 (3.7)	27.2 (3.7)	26.3 (3.6)	27.2 (3.9)	26.8 (3.8)	26.1 (3.6)
Total energy intake (kcal/day)[a]	2,241 (636)	2,543 (691)	2,271 (641)	2,634 (689)	2,241 (636)	2,543 (691)	2,232 (628)	2,633 (755)
Alcohol intake (%)								
Never	0.8	2.7	0.6	2.6	2.3	1.0	1.3	0.9
Former drinker	2.4	5.4	2.5	5.5	7.1	2.6	2.9	3.3
Current drinker	1.0	7.0	1.4	4.8	1.4	4.2	3.0	2.9
Past and current drinker	53.2	80.7	65.1	77.4	63.4	66.6	80.3	53.9
Not specified	42.7	4.3	30.4	9.6	25.9	25.7	12.6	39.1
Smoking habits (%)								
Never	34.5	30.9	28.9	33.7	34.5	30.9	27.7	37.7
Former smoker	32.6	36.5	32.6	37.6	32.6	36.5	37.3	33.0
Current smoker	32.0	29.8	37.6	26.5	32.0	29.8	34.0	27.9
Not specified	0.9	2.9	0.9	2.1	0.9	2.9	1.0	1.4
Education (%)								
None	1.5	10.3	2.0	9.2	1.5	10.3	5.6	1.4
Primary school	34.6	31.6	29.7	34.2	34.6	31.6	33.6	28.3
Technical/professional school	26.2	18.3	27.9	18.2	26.2	18.3	22.8	26.7
Secondary school	15.3	11.1	12.9	13.7	15.3	11.1	12.1	14.3
University degree	21.9	25.8	26.2	23.0	21.9	25.8	24.8	26.7
Not specified	0.5	2.9	1.4	1.7	0.5	2.9	1.1	2.7
Physical activity (%)								
Low	15.9	17.8	19.4	18.3	15.9	17.8	21.2	13.4
Medium	22.9	29.0	24.4	28.3	22.9	29.0	28.6	22.1
High	25.7	38.6	29.1	36.1	25.7	38.6	34	31.2
Very high	9.1	13.1	11.2	14.4	9.1	13.1	11.8	13.1
Not specified	26.5	1.5	15.9	2.9	26.5	1.5	4.4	20.2

BMI = body mass index; EPIC = European Prospective Investigation into Cancer and Nutrition; Q = quintile.
[a]Mean (SD).
[b]Weight (kg)/height (m)^2.

TABLE 3

Baseline characteristics of female participants by lowest and highest intake (g/day) categories of red meat, processed meat, poultry, fish, fruits, vegetables, and nuts and seeds, EPIC study, follow-up 1992–2010

		Red meat		Processed meat		Poultry		Fish	
Characteristic	Total cohort	1thQ (0–12.1)	5thQ (70.4–722.2)	1thQ (0–7.4)	5thQ (50–770.8)	1thQ (0–3.4)	5thQ (31.4–690)	1thQ (0–6.2)	5thQ (45.2–755.6)
Age at recruitment, yr[a]	50.8 (9.8)	47.9 (11.7)	52.2 (8.7)	49.5 (12.8)	49.8 (8.4)	49.2 (11.8)	51.3 (9.3)	47.7 (12.2)	50.9 (8.0)
BMI at baseline [a,b]	25.0 (4.4)	24.0 (4.2)	25.3 (4.6)	24.9 (4.7)	25.4 (4.6)	23.9 (4.0)	25.9 (4.8)	24.5 (4.3)	25.1 (4.4)
Total energy intake (kcal/day)[a]	1,931 (540)	1,762 (524)	2,231 (547)	1,780 (498)	2,195 (580)	1,843 (530)	2,115 (568)	1,790 (500)	2,008 (566)
Alcohol intake (%)									
Never	7.9	6.7	7.5	12.6	5.2	5.7	12.7	5.6	8.1
Former drinker	3.7	3.3	3.5	4.6	3.1	2.4	6.4	2.8	4.2
Current drinker	11.6	15.3	12.3	19.3	6.6	14.6	14.9	9.9	9.9
Past and current drinker	52.7	51.3	63.7	53.7	52.8	50.2	58.8	48.1	38.8
Not specified	24.1	23.5	13.1	9.8	32.3	27.1	7.2	33.6	38.9
Smoking habits (%)									
Never	55.7	59.3	54.1	62.3	52.0	55.8	61.6	53.6	51.8
Former smoker	22.5	23.9	21.9	20.9	22.3	23.8	20.3	24.4	23.6
Current smoker	19.5	14.4	21.6	14.8	23.1	17.9	15.8	21.2	21.0
Not specified	2.3	2.4	2.4	2.1	2.7	2.5	2.3	0.8	3.6
Education (%)									
None	4.6	4.5	2.3	8.5	3.8	1.3	9.4	2.5	6.5
Primary school	24.2	15.5	25.4	20.8	25.8	18.5	27.8	20.3	23.7
Technical/professional school	21.8	20.4	20.7	17.0	25.8	21.5	15.6	27.0	21.1
Secondary school	23.9	23.1	28.0	20.2	23.1	24.6	22.6	22.1	25.8
University degree	23.0	31.9	21.8	29.0	20.6	30.6	21.0	25.7	20.6
Not specified	2.5	4.6	1.9	4.6	1.0	3.5	3.7	2.8	2.3
Physical activity (%)									
Low	13.6	14.9	15.2	14.8	13.1	15.9	13.9	13.8	9.4
Medium	31.6	31.6	39.8	31.2	30.3	36.0	34.7	26.8	25.4
High	33.0	29.0	33.9	41.1	28.8	28.0	41.9	33.4	27.0
Very high	6.5	5.9	8.1	8.9	5.1	6.3	7.3	9.2	4.1
Not specified	15.3	18.6	3.0	4.0	22.8	13.2	2.1	16.8	34.2

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TABLE 3
Baseline characteristics of female participants by lowest and highest intake (g/day) categories of red meat, processed meat, poultry, fish, fruits, vegetables and nuts and seeds, EPIC study, follow-up 1992–2010 *(Continued)*

	Nuts and seeds		Fruit		Vegetables		Dairy products	
	1thQ (0)	5thQ (5.34–286.1)	1thQ (0–91.1)	5thQ (346.6–4646.8)	1thQ (0–97.8)	5thQ (307–2979.3)	1thQ (0–134.1)	5thQ (490.2–4566.1)
Age at recruitment, yr[a]	50.3 (9.5)	51.2 (10.5)	48.9 (9.6)	51.7 (9.9)	50.3 (9.5)	51.2 (10.5)	50.4 (9.5)	51.6 (10.4)
BMI at baseline [a,b]	25.0 (4.4)	25.3 (4.7)	24.6 (4.4)	25.5 (4.6)	25.0 (4.4)	25.3 (4.7)	25.1 (4.6)	24.9 (4.3)
Total energy intake (kcal/day)	1,684 (474)	2,127 (569)	1,728 (499)	2,133 (564)	1,684 (474)	2,127 (569)	1,694 (485)	2,177 (626)
Alcohol intake (%)								
Never	6.2	11.8	4.8	12.8	15.3	4.7	8.0	7.4
Former drinker	3.0	4.6	2.8	5.4	6.7	2.7	3.1	4.2
Current drinker	4.6	20.6	7.4	15.6	7.5	13.5	10.0	13.3
Past and current drinker	42.6	56.5	49.7	52.8	34.1	61.3	51.6	51.8
Not specified	43.6	6.5	35.2	13.5	36.4	17.9	27.4	23.4
Smoking habits (%)								
Never	49.1	62.4	42.7	63.1	49.1	62.4	51.4	55.9
Former smoker	21.5	21.1	21.8	21.1	21.5	21.1	21.8	23.5
Current smoker	27.8	13.2	33.2	13.7	27.8	13.2	24.5	18.6
Not specified	1.7	3.3	2.4	2.2	1.7	3.3	2.2	2.0
Education (%)								
None	3.2	7.5	2.8	7.9	3.2	7.5	5.9	2.7
Primary school	32.2	20.8	24.8	27.3	32.2	20.8	27.8	21.9
Technical/professional school	29.3	12.2	28.6	15.1	29.3	12.2	23.2	25.4
Secondary school	19.4	27.1	22.1	24.3	19.4	27.1	21.0	22.7
University degree	15.4	28.1	19.6	22.6	15.4	28.1	19.8	23.4
Not specified	0.6	4.3	2.2	2.8	0.6	4.3	1.5	4.0
Physical activity (%)								
Low	12.1	12.8	15.4	11.5	12.1	12.8	14.0	12.2
Medium	22.7	37.7	28.4	31.9	22.7	37.7	27.9	32.0
High	27.5	38.5	24.7	42.4	27.5	38.5	32.3	35.0
Very high	4.8	7.8	5.0	8.5	4.8	7.8	6.0	8.7
Not specified	32.9	3.2	26.6	5.7	32.9	3.2	19.7	12.1

BMI = body mass index; EPIC = European Prospective Investigation into Cancer and Nutrition; Q = quintile.
[a]Mean (SD).
[b]Weight (kg)/height $(m)^2$.

TABLE 4
Association between dietary intakes and risk of total leukemia and leukemia subtypes, EPIC study, follow-up 1992–2010

	All leukemias ($N = 773$)			Myeloid leukemia ($n = 342$)			Lymphoid leukemia ($n = 373$)		
Dietary intake[a] g/day	*N*	HR	95% CI	*N*	HR	95% CI	*N*	HR	95% CI
Red meat									
Q1: 4.6 (0–12.10)	118	1.00		54	1.00		56	1.00	
Q2: 19.7 (12.1–26.8)	151	1.09	0.85–1.41	68	1.14	0.78–1.68	67	0.98	0.66–1.47
Q3: 35.3 (26.84–44.56)	163	1.11	0.85–1.44	84	1.34	0.91–1.96	72	0.98	0.65–1.48
Q4: 56.6 (44.57–70.37)	155	1.02	0.77–1.34	53	0.84	0.54–1.29	90	1.10	0.73–1.69
Q5: 99.3 (70.38–722.20)	186	1.09	0.81–1.46	83	1.27	0.82–1.97	88	0.96	0.61–1.51
P-trend			0.83			0.74			0.95
Uncalibrated (50 g/day)		0.96	0.85–1.09		0.98	0.82–1.18		0.92	0.76–1.10
Calibrated (50 g/day)		0.98	0.79–1.22		1.06	0.76–1.49		0.89	0.65–1.22
Poultry									
Q1: 0.6 (0–3.42)	163	1.00		72	1.00		80	1.00	
Q2: 7.0 (3.43–9.99)	149	0.84	0.66–1.07	67	1.02	0.71–1.48	69	0.71	0.49–1.03
Q3: 14.3 (10.00–17.11)	172	0.97	0.77–1.22	84	1.20	0.85–1.70	79	0.87	0.61–1.26
Q4: 23.4 (17.12–31.36)	130	0.77	0.60–1.00	49	0.79	0.53–1.18	69	0.71	0.49–1.05
Q5: 50.2 (31.37–690.00)	159	0.95	0.74–1.22	70	1.03	0.71–1.50	76	0.90	0.61–1.31
P-trend			0.60			0.71			0.68
Uncalibrated (50 g/day)		0.91	0.74–1.12		0.90	0.66–1.23		0.88	0.65–1.19
Calibrated (50 g/day)		0.78	0.54–1.12		0.72	0.42–1.24		0.65	0.39–1.11
Processed meat									
Q1: 2.5 (0–7.37)	124	1.00		55	1.00		57	1.00	
Q2: 13.1 (7.38–18.54)	151	0.97	0.75–1.27	72	1.17	0.78–1.74	70	0.82	0.54–1.23
Q3: 24.4 (18.55–30.96)	157	1.01	0.78–1.32	71	1.18	0.78–1.78	70	0.90	0.60–1.36
Q4: 39.4 (30.97–49.94)	150	0.96	0.73–1.28	63	1.05	0.68–1.62	77	0.92	0.61–1.42
Q5: 78.8 (49.95–770.84)	191	1.10	0.82–1.48	81	1.23	0.78–1.92	99	1.16	0.75–1.81
P-trend			0.53			0.63			0.27
Uncalibrated (50 g/day)		1.05	0.92–1.20		1.05	0.74–1.50		1.19	1.00–1.42
Calibrated (50 g/day)		1.08	0.85–1.35		1.03	0.92–1.16		1.29	0.93–1.77
Offals[b]									
Q1: 0	398	1.00		182	1.00		184	1.00	
Q2: 0.4 (0.005–0.66)	88	0.95	0.72–1.27	40	0.87	0.57–1.32	40	1.07	0.70–1.63
Q3: 2.2 (0.67–3.92)	146	0.80	0.64–0.99	58	0.81	0.57–1.14	76	0.81	0.60–1.10
Q4: 10.9 (3.93–227.61)	141	0.91	0.73–1.14	62	0.97	0.69–1.36	73	0.94	0.69–1.30
P-trend			0.17			0.62			0.37
Uncalibrated (5 g/day)		0.97	0.89–1.06		1.03	0.92–1.16		0.95	0.84–1.08
Calibrated (5 g/day)		0.93	0.83–1.04		0.87	0.72–1.05		0.96	0.83–1.12
Fish									
Q1: 1.9 (0–6.17)	148	1.00		60	1.00		78	1.00	
Q2: 11.0 (6.18–16.10)	155	1.06	0.83–1.34	68	1.27	0.88–1.84	71	0.87	0.61–1.25
Q3: 21.5 (16.11–26.82)	166	1.07	0.84–1.37	81	1.44	0.99–2.10	74	0.84	0.57–1.23
Q4: 34.9 (26.83–45.21)	145	0.91	0.70–1.19	55	0.98	0.65–1.48	78	0.85	0.57–1.26
Q5: 77.7 (45.21–755.64)	159	1.09	0.83–1.44	78	1.50	0.99–2.26	72	0.91	0.60–1.39
P-trend			0.96			0.27			0.68
Uncalibrated (50 g/day)		1.00	0.86–1.15		1.04	0.84–1.27		1.01	0.81–1.26
Calibrated (50 g/day)		1.08	0.84–1.40		1.02	0.68–1.51		1.10	0.76–1.60

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TABLE 4
Association between dietary intakes and risk of total leukemia and leukemia subtypes, EPIC study, follow-up 1992–2010
(Continued)

	All leukemias ($N = 773$)			Myeloid leukemia ($n = 342$)			Lymphoid leukemia ($n = 373$)		
Dietary intake[a] g/day	*N*	HR	95% CI	*N*	HR	95% CI	*N*	HR	95% CI
Fruit									
Q1: 49.9 (0–91.09)	174	1.00		73	1.00		88	1.00	
Q2: 122.4 (91.10–156.01)	153	0.92	0.74–1.15	65	0.88	0.62–1.24	71	0.86	0.62–1.21
Q3: 194.9 (156.02–237.31)	155	0.97	0.78–1.22	70	0.96	0.68–1.35	78	1.02	0.73–1.43
Q4: 286.0 (237.32–346.61)	135	0.95	0.74–1.21	58	0.86	0.59–1.24	68	1.03	0.72–1.49
Q5: 509.2 (346.62–4646.8)	156	1.13	0.88–1.45	76	1.13	0.78–1.64	68	1.04	0.71–1.53
P-trend			0.39			0.61			0.59
Uncalibrated (50 g/day)		1.01	0.97–1.06		1.01	0.94–1.08		1.02	0.96–1.09
Calibrated (100 g/day)		1.05	0.97–1.14		1.07	0.95–1.20		1.05	0.94–1.17
Nuts/seeds									
Q1: 0	238	1.00		107	1.00		115	1.00	
Q2: 0.2 (0.01–0.48)	90	1.01	0.81–1.25	44	1.09	0.78–1.52	41	1.03	0.73–1.44
Q3: 1.0 (0.49–1.97)	187	0.99	0.79–1.25	71	0.87	0.61–1.25	100	1.32	0.95–1.85
Q4: 3.5 (1.98–5.33)	130	1.04	0.81–1.34	59	1.19	0.83–1.73	62	1.17	0.80–1.71
Q5: 15.5 (5.34–286.06)	128	1.08	0.81–1.44	61	1.12	0.73–1.72	55	1.20	0.77–1.87
P-trend			0.62			0.57			0.25
Uncalibrated (5 g/day)		0.96	0.89–1.03		1.04	0.98–1.10		1.04	0.94–1.16
Calibrated (5 g/day)		0.96	0.80–1.15		1.04	0.89–1.20		1.04	0.80–1.34
Vegetables									
Q1: 65.6 (0–97.84)	180	1.00		72	1.00		91	1.00	
Q2: 121.8 (97.85–146.58)	171	0.73	0.53–0.99	80	0.81	0.51–1.28	76	0.73	0.45–1.20
Q3: 175.9 (146.59–208.51)	158	0.89	0.71–1.12	62	0.82	0.58–1.17	88	0.90	0.65–1.26
Q4: 252.8 (208.52–306.97)	142	0.97	0.76–1.23	71	0.96	0.67–1.37	65	1.00	0.69–1.44
Q5: 440.2 (306.98–2979.3)	122	1.11	0.86–1.42	57	1.18	0.81–1.71	53	1.00	0.67–1.48
P-trend			0.40			0.47			0.87
Uncalibrated (100 g/day)		1.02	0.98–1.06		0.96	0.86–1.07		1.00	0.93–1.07
Calibrated (100 g/day)		1.06	0.97–1.16		0.97	0.74–1.27		1.07	0.94–1.22
Dairy products									
Q1: 75 (0–134.1)	148	1.00		63	1.00		70	1.00	
Q2: 183 (134.2–228.5)	135	1.04	0.82–1.32	58	1.03	0.71–1.48	67	1.12	0.80–1.57
Q3: 278.6 (228.6–332.3)	158	1.10	0.87–1.38	77	1.26	0.89–1.78	70	0.99	0.70–1.39
Q4: 404.5 (332.4–490.1)	151	1.01	0.79–1.28	72	1.03	0.71–1.48	68	1.01	0.71–1.44
Q5: 691 (490.2–4566.1)	181	1.01	0.79–1.28	72	0.91	0.62–1.33	98	1.14	0.81–1.60
P-trend			0.93			0.61			0.65
Uncalibrated (100 g/day)		1.00	0.97–1.03		0.98	0.93–1.03		1.02	0.98–1.06
Calibrated (100 g/day)		0.99	0.95–1.04		0.97	0.90–1.05		1.02	0.96–1.09

CI = confidence interval; EPIC = European Prospective Investigation into Cancer and Nutrition; HR = hazard ratio; Q = quintile. $P < 0.05$ is two-sided. Multivariate models adjusted for body mass index, education, smoking, alcohol intake, physical activity and total energy intake and stratified by sex, center and age at recruitment; *P*-trends were tested by assigning a score ranging from 1 to 5 according to the quintile categories for and entering them as a continuous term in the regression models.

[a]Mean intake (minimum-maximum).

[b]Quartile categorization was assigned to the offals intake variable.

TABLE 5
Association between dietary intakes and risk of leukemia subtypes: AML, CML and CLL in the EPIC study, follow-up 1992–2010

	Multivariate model								
	Acute myeloid leukemia ($N = 187$)			Chronic myeloid leukemia ($n = 80$)			Chronic lymphoid leukemia ($n = 333$)		
Dietary intake[a] g/day	*N*	HR	95% CI	*N*	HR	95% CI	*N*	HR	95% CI
Red meat									
Q1: 6.6 (0–16.0)	42	1.00		21	1.00		61	1.00	
Q2: 25.3 (16.1–34.7)	45	0.99	0.63–1.55	27	1.13	0.61–2.11	85	1.20	0.84–1.70
Q3: 47.8 (34.8–63.04)	46	1.05	0.65–1.70	16	0.68	0.32–1.44	82	0.99	0.68–1.46
Q4: 92.7 (63.05–722.2)	54	1.10	0.66–1.84	16	0.76	0.33–1.73	105	1.01	0.67–1.53
P-trend			0.68			0.31			0.77
Uncalibrated (50 g/day)		1.04	0.82–1.32		0.83	0.53–1.31		0.96	0.79–1.16
Calibrated (50 g/day)		1.01	0.63–1.62		1.22	0.59–2.52		0.93	0.67–1.29
Poultry									
Q1: 1.4 (0–5.9)	47	1.00		20	1.00		84	1.00	
Q2: 9.7 (6.0–15)	44	1.00	0.64–1.56	18	0.96	0.48–1.91	88	0.88	0.64–1.21
Q3: 19.3 (15.1–27.2)	49	1.01	0.65–1.56	22	1.23	0.63–2.41	79	0.80	0.57–1.12
Q4: 45.9 (27.3–690)	47	1.02	0.65–1.61	20	1.06	0.52–2.16	82	0.91	0.65–1.28
P-trend			0.92			0.73			0.51
Uncalibrated (50 g/day)		1.01	0.68–1.48		0.97	0.51–1.83		0.90	0.66–1.23
Calibrated (50 g/day)		0.83	0.40–1.69		0.67	0.20–2.27		0.67	0.39–1.17
Processed meat									
Q1: 3.8 (0–10.5)	45	1.00		14	1.00		63	1.00	
Q2: 17.3 (10.6–24.2)	59	1.07	0.71–1.63	23	1.46	0.69–3.10	83	1.02	0.72–1.45
Q3: 33.2 (24.3–43.8)	32	0.59	0.36–0.97	21	1.30	0.59–2.88	83	0.98	0.68–1.41
Q4: 72.4 (43.9–770.8)	51	0.88	0.53–1.46	22	1.24	0.53–2.92	104	1.23	0.83–1.82
P-trend			0.90			0.81			0.32
Uncalibrated (50 g/day)		0.75	0.54–1.04		1.08	0.71–1.66		1.17	0.97–1.42
Calibrated (50 g/day)		0.82	0.49–1.35		0.67	0.31–1.46		1.23	0.87–1.72
Offals									
Q1: 0	100	1.00		44	1.00		165	1.00	
Q2: 0.4 (0.005–0.66)	24	0.98	0.56–1.71	11	1.18	0.50–2.78	36	1.04	0.67–1.63
Q3: 2.2 (0.67–3.92)	26	0.69	0.42–1.12	18	0.99	0.50–1.98	64	0.73	0.53–1.01
Q4: 10.9 (3.93–227.61)	37	0.99	0.64–1.54	7	0.55	0.22–1.33	68	0.96	0.69–1.33
P-trend			0.62			0.27			0.49
Uncalibrated (5 g/day)		1.03	0.88–1.21		0.69	0.43–1.10		0.97	0.84–1.10
Calibrated (5 g/day)		0.92	0.71–1.19		0.72	0.47–1.09		0.95	0.80–1.12
Fish									
Q1: 3.0 (0–8.2)	35	1.00		23	1.00		86	1.00	
Q2: 14.9 (8.3–21.0)	46	1.52	0.93–2.48	20	0.98	0.51–1.91	77	0.92	0.65–1.29
Q3: 29.3 (21.1–38.9)	49	1.56	0.87–2.43	11	0.51	0.23–1.16	93	0.95	0.66–1.35
Q4: 70.6 (40–755.6)	57	1.75	1.02–2.97	26	1.29	0.62–2.66	77	0.87	0.59–1.29
P-trend			0.07			0.78			0.57
Uncalibrated (50 g/day)		1.10	0.86-1.41		1.08	0.71–1.63		1.00	0.79–1.27
Calibrated (50 g/day)		1.10	0.65–1.87		0.98	0.42–2.28		1.21	0.82–1.77

(Continued on next page)

TABLE 5
Association between dietary intakes and risk of leukemia subtypes: AML, CML and CLL in the EPIC study, follow-up 1992–2010 *(Continued)*

	Multivariate model								
	Acute myeloid leukemia ($N = 187$)			Chronic myeloid leukemia ($n = 80$)			Chronic lymphoid leukemia ($n = 333$)		
Dietary intake[a] g/day	*N*	HR	95% CI	*N*	HR	95% CI	*N*	HR	95% CI
Fruit									
Q1: 59.6 (0–106)	46	1.00		23	1.00		95	1.00	
Q2: 148.1 (106.1–193.4)	48	1.06	0.70–1.63	21	0.87	0.47–1.60	88	1.04	0.77–1.41
Q3: 248.9 (193.5–313.2)	41	0.96	0.60–1.52	18	0.71	0.37–1.38	73	0.98	0.71–1.37
Q4: 473.3 (313.3–4646.8)	52	1.30	0.81–2.07	18	0.63	0.31–1.31	77	1.18	0.83–1.67
P-trend			0.36			0.18			0.47
Uncalibrated (100 g/day)		1.00	0.91–1.09		0.97	0.84–1.13		1.02	0.95–1.10
Calibrated (100 g/day)		1.08	0.92–1.27		0.99	0.74–1.25		1.05	0.93–1.18
Nuts/seeds									
Q1: 0	59	1.00		23	1.00		103	1.00	
Q2: 0.4 (0.01–0.7)	41	0.69	0.43–1.13	20	0.75	0.35–1.59	96	0.86	0.62–1.21
Q3: 2.4 (0.8–4)	42	0.94	0.60–1.47	23	1.50	0.79–2.84	74	0.94	0.68–1.32
Q4: 13.2 (4.1–286.1)	45	1.27	0.79–2.04	14	1.06	0.49–2.29	60	0.97	0.67–1.41
P-trend			0.20			0.40			0.94
Uncalibrated (5 g/day)		1.03	0.96–1.11		1.08	0.87–1.34		1.01	0.91–1.13
Calibrated (5 g/day)		1.02	0.83–1.23		1.54	0.91–2.59		1.02	0.77–1.34
Vegetables									
Q1: 73.2 (0–109.7)	49	1.00		23	1.00		93	1.00	
Q2: 140.9 (109.8–175)	46	0.90	0.59–1.37	21	0.96	0.51–1.79	94	1.20	0.89–1.62
Q3: 220.5 (175.1–276)	51	1.03	0.66–1.59	20	1.13	0.59–2.19	86	1.26	0.91–1.75
Q4: 410.3 (276.1–2979.3)	41	1.05	0.63–1.75	16	1.24	0.57–2.71	60	1.22	0.82–1.82
P-trend			0.76			0.55			0.23
Uncalibrated (100 g/day)		0.94	0.82–1.09		1.07	0.97–1.19		1.00	0.93–1.08
Calibrated (100 g/day)		0.77	0.53–1.14		1.26	0.95–1.66		1.06	0.93–1.22
Dairy products									
Q1: 89.5 (0–160.6)	42	1.00		17	1.00		79	1.00	
Q2: 217.8 (160.7–277)	40	0.99	0.63–1.54	25	1.72	0.91–3.28	79	1.09	0.79–1.49
Q3: 352.1 (277.1–444.7)	46	0.91	0.58–1.42	18	1.22	0.60–2.50	68	0.84	0.60–1.18
Q4: 646.2 (444.8–4566.1)	59	1.00	0.64–1.56	20	1.27	0.61–2.67	107	1.09	0.79–1.51
P-trend			0.94			0.79			0.88
Uncalibrated (100 g/day)		0.96	0.90–1.03		1.03	0.93–1.14		1.00	0.96–1.05
Calibrated (100 g/day)		0.95	0.86–1.06		1.04	0.88–1.23		1.00	0.93–1.08

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; HR, hazard ratio; *N*, number; Q, quartile.

$P < 0.05$ is two-sided.

[a]Mean intake (minimum-maximum).

Multivariate models adjusted for body mass index, education, smoking, alcohol intake, physical activity and total energy intake and stratified by sex, center and age at recruitment; *P*-trends were tested by assigning a score ranging from 1 to 4 according to the quartile categories for and entering them as a continuous term in the regression models.

misclassification among those who changed their dietary pattern during the follow-up period. This misclassification is likely to be nondifferential and as such would attenuate the strength of any true association. In addition, the power to explore possible associations with some leukemia subtypes was low possibly resulting in false-negative results.

In conclusion, our study did not support a possible link between dietary factors and lymphoid and myeloid leukemia risk in adult. Lack of any association for most dietary variables examined in this large and well-conducted prospective study suggests that intake of total vegetables, total fruits, total nuts/seeds, total dairy products, red meat, processed meat, poultry, offals, and fish are unlikely to play a major role in the development of leukemias and leukemia subtypes.

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SUPPLEMENTAL MATERIAL

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