# Fruit and vegetable consumption and lymphoma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC)

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## Abstract

*Introduction* Lymphomas are a heterogeneous group of malignant diseases of cells of the immune system. The best-established risk factors are related to dys-regulation of immune function, and evidence suggests that factors such as dietary or lifestyle habits may be involved in the etiology.

*Material and methods* In the European Prospective Investigation into Cancer and Nutrition (EPIC), 849 lymphoma cases were identified in a median follow-up period

The work described in this article was carried out with the financial support of: Europe Against Cancer Program of the European Commission (SANCO); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum, German Federal Ministry of Education and Research; Danish Cancer Society; Health Research Fund (FIS) of the Spanish Ministry of Health, Spanish Regional Governments of Andalucia, Asturia, Basque Country, Murcia and Navarra; the ISCIII Network RCESP (C03/09), Spain; Cancer Research UK; Medical Research Council, United Kingdom; Stroke Association, United Kingdom; British Heart Foundation; Department of Health, United Kingdom; Food Standards Agency, United Kingdom; Wellcome Trust, United Kingdom; Greek Ministry of Health; Greek Ministry of Education; Italian Association for Research on Cancer (AIRC); Italian National Research Council, Fondazione-Istituto Banco Napoli, Italy; Compagnia di San Paolo; Dutch Ministry of Public Health, Welfare and Sports; World Cancer Research Fund; Swedish Cancer Society; Swedish Scientific Council; Regional Government of Skåne, Sweden; Norwegian Cancer Society; Research Council of Norway; French League against Cancer (LNCC); National Institute for Health and Medical Research (INSERM), France; Mutuelle Générale de l'Education Nationale (MGEN), France; 3M Co, France; Gustave Roussy Institute (IGR), France; and General Councils of France.

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of 6.4 years. Fruit and vegetable consumption was estimated from validated dietary questionnaires. Cox proportional hazard models were used to examine the association between fruit and vegetable intake with the risk of lymphomas overall and subentities.

*Results* There was no overall association between total fruit and vegetable consumption and risk of lymphoma [hazard ratio (HR) = 0.95, 95% confidence interval (CI) 0.78–1.15 comparing highest with lowest quartile]. However, the risk of diffuse large B-cell lymphomas (DLBCL) tended to be lower in participants with a high intake of total vegetables (HR = 0.49, 95% CI 0.23–1.02).

*Conclusion* In this large prospective study, an inverse associations between fruit and vegetable consumption and risk of lymphomas overall could not be confirmed. Associations with lymphoma subentities such as DLBCL warrant further investigation.

**Keywords** Non-Hodgkin lymphoma · Hodgkin lymphoma · Fruits · Vegetables · Cohort study

## Introduction

Lymphomas are a heterogeneous group of malignant diseases of cells of the immune system. In 2004, they represented the 7th most common cancer in Europe with 121,200 incident cases and 65,200 estimated deaths [1]. While the evolution of incidence of Hodgkin lymphoma (HL) appears to be stable, the incidence of non-Hodgkin lymphoma (NHL) is increased in recent years, but the reasons are unclear [2].

The best established risk factors are related to up- and down-regulation of immune function, either genetically determined or acquired such as, e.g., in immune deficiency

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due to HIV infection or in immune suppression when iatrogenically induced after transplantation [3]. However, evidence suggests that also other factors including lifestyle habits such as smoking and alcohol consumption might affect lymphoma risk. While heavy smoking appears to increase the risk, indications of a decreased risk for moderate alcohol consumption were found [4, 5]. With respect to dietary habits, 12 case–control studies, among them six population-based [6–11] and six hospital-based [12–17], and two cohort studies [18, 19] examined the association between fruit and vegetable consumption and lymphoma risk. The strongly diverging results ranged from inverse associations over no effects even to risk elevation with a high consumption of fruits and vegetable.

Case–control studies have the potential limitation that lifestyle habits are determined after the cancer has been diagnosed that may introduce recall bias. Thus, it is of basic interest to examine published associations also in a prospective design. The European Prospective Investigation into Cancer and Nutrition (EPIC) is a large European effort to explore the role of dietary and other lifestyle habits in the aetiology of cancer and offers opportunity to investigate lymphoma risk with respect to fruit and vegetable intake.

## Methods

### Population

EPIC is a large prospective cohort study conducted since 1992 in 23 centers in ten European countries [Denmark (Aarhus, Copenhagen), France, Germany (Heidelberg, Potsdam), Great Britain (Cambridge, Oxford), Greece, Italy (Florence, Varese, Ragusa, Turin, Naples), Norway, Spain (Asturias, Granada, Murcia, Navarra, San Sebastian), Sweden (Malmö, Umea), The Netherlands (Bilthoven, Utrecht)] with 521,457 participants. In most centers, the participants were recruited from the general population. However, French participants were female members of a health insurance for school and university employees. Spanish and Italian participants were recruited among blood donors, members of several health insurance programs, employees of several enterprises, civil servants, but also the general population. In Utrecht, participants in mammographic screening programs were recruited for the study, and the cohort in Florence also recruited participants of such screening programs. In Oxford, half of the cohort consisted of ‘health conscious’ subjects from England, Wales, Scotland, and Northern Ireland. This group includes vegans, ovo-lacto vegetarians, fish eaters (consuming fish but no meat), and meat eaters. The cohorts of France, Norway, Utrecht, and Naples include women only [20].

Of the 521,457 participants, we excluded prevalent cancer cases ($n$ = 23,722), subjects with incomplete dietary, non-dietary, or follow-up information ($n$ = 9,296), or with a ratio for energy intake versus energy expenditure in the top and bottom 1% ($n$ = 8,319). We also excluded the French cohort ($n$ = 69,023) because lymphomas have not been assessed. Finally, four uncertain lymphoma cases were excluded from the analysis. Thus, the current analysis was based on 411,097 EPIC participants, among whom 849 incident lymphoma cases occurred.

### Exposure assessment

Diet over the previous 12 months was assessed using dietary assessment instruments that were specifically developed for each participating country based on a common core protocol [20]. Questions were structured by meals on the questionnaires used in Italy and Spain, and by broad food groups in the other centers. The number of questions on fruit and vegetable intake varied by center, thus, reflecting the usual variety of these foods available to participants. Participants were asked to report their average consumption of each food over the previous 12 months, according to pre-coded categories ranging from never or less than once per month to six or more times per day. Individual average portions were estimated in Germany, Italy, The Netherlands, and Spain, whereas standard portions were assigned to all subjects in Denmark, the United Kingdom, Norway, and Umeå, and a combination of methods for estimating portion size was used in Malmo. All dietary measurement instruments have been validated previously in a series of studies within the various source populations participating in EPIC [21].

Fruits and vegetables were grouped into total vegetables, fruiting vegetables, root vegetables, leafy vegetables, cabbages, mushrooms, grain and pod vegetables, garlic and onions, stalk vegetables and sprouts, total fruits, citrus fruits, apples and pears, grapes, stone fruits, berries, total fruit and vegetable juices and citrus fruit juices (see Appendix). Details of food items included in the selected vegetable subgroups used in the present analysis have been reported previously [22]. In the tables, we present a selection of the above-mentioned fruit and vegetable subgroups, which were the most frequently consumed groups (total vegetables, fruiting vegetables, leafy vegetables, cabbages, garlic and onions, total fruits, hard fruits, citrus fruits). Results of other food groups are mentioned in the text. Lifestyle questionnaires were used to collect information on education, medical history (surgeries and previous illnesses), tobacco and alcohol consumption, and physical activity. Height and weight were measured at the baseline examination, except for Norway, and Oxford,

where self-reported height and weight was assessed via questionnaire [20].

### Outcome assessment

Cancer diagnoses were based on population registries in Denmark, Italy, The Netherlands, Norway, Spain, Sweden, and the United Kingdom. An active follow-up through study subjects as well as next-to-kin information, the use of health insurance records and cancer and pathology registries were used in Germany and Greece. Mortality data were also obtained from either the cancer or mortality registries at the regional or national level. Censoring dates for complete follow-up were as follows: December 1999 (Turin); June 2000 (Bilthoven); December 2000 (Asturias, Murcia, Cambridge); December 2001 (Florence, Varesa, Ragusa, Naples, Granada, Navarra, San Sebastian, Oxford, Malmö, Norway); June 2002 (France); December 2002 (Umea, Aarhus, Copenhagen); June 2003 (Utrecht). For Germany and Greece, the end of the follow up was considered to be the last known contact, the date of diagnosis or the date of death, whichever came first. Currently, vital status is known for 98.4% of all EPIC subjects.

The diagnosis of lymphoma cases was based on the 2nd revision of the International Classification of Diseases for Oncology (ICD-O-2). However, because a new WHO classification of tumors of the hematopoietic and lymphoid tissues was developed [23] and is internationally widely used, we reclassified all lymphoma cases into ICD-O-3, which is based on this WHO classification. Briefly, we used a conversion program available on the web side of the SEER program, and involved a pathology expert (T.R.) as well as experts from the EPIC centers (see Appendix). Since not all ICD-O-2 diagnostics can be translated unequivocally into a lymphoma diagnosis according to the WHO system, we left the respective lymphomas unclassified (''nos'') when further detailed specification failed (22.9%).

In the current analysis, the following groups were considered: all lymphoma combined, HL, and NHL; within NHL the B-cell lymphoma (B-NHL) and T-cell lymphoma (T-NHL), and among B-NHL the entities diffuse large B-cell lymphomas (DLBCL), follicular lymphomas (FL), B-cell chronic lymphocytic leukemia (BCLL), and multiple myeloma/plasmacytoma (MM). Other entities were not considered because of small numbers (Table 1).

### Statistical analysis

Cox proportional hazards regression was used to examine the association of fruit and vegetable consumption with lymphomas entering fruit and vegetable consumption as categorical variables by quartiles of intake into the models. Age was used as the primary time variable in the Cox models. Time at entry was age at recruitment, exit time was age when participants were diagnosed with cancer, died, were lost to follow-up, or were censored at the end of the follow-up period, whichever came first. The analyses were stratified by center, gender, and age at recruitment in one-year categories. In our regression models, we adjusted for cigarette smoking [never, former (2 categories), current (3 categories), other, missing], education (no degree or primary school completed, technical or professional school completed; secondary school completed; university degree; not specified or missing), alcohol consumption at baseline (4 categories), and energy intake. Height, weight, and physical activity did not alter the associations and were not included in the final Cox regression models. Trend tests were performed by assigning a score ranging from 1 to 4 according to a participant's quartile of intake of the respective food item as a continuous variable into the Cox regression model.

In order to improve the comparability of dietary data across the participating centers, dietary intakes from the questionnaires were calibrated using a 24-h dietary recall that was standardized across centers [24, 25]. This information was used to calibrate dietary measurements across countries, thus, partly correcting for over- and underestimation of dietary intakes [26, 27]. In brief, an 8% random sample of each center's participants provided a 24-h dietary recall. Dietary intakes were calibrated using a fixed effects linear model in which gender- and center-specific 24-h dietary recall data were regressed on the questionnaire data controlling for weight, height, age, day of the week, and season of the year. Non-consumers of a specific food group were excluded from the regression calibration models and kept as zero values. Calibrated and uncalibrated data was used to estimate the association of fruit and vegetable consumption on a continuous scale.

Sub-analyses were performed by sex and smoking status. We tested for interaction between by including a cross-product term along with the main effect terms in the Cox regression model. The statistical significance of the cross-product term was evaluated using the likelihood ratio test. We also examined whether the association was altered by excluding the first two years of follow-up. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, North Carolina).

## Results

In this analysis 849 lymphoma cases (414 in men, 435 in women) were included. Of these, 801 were NHL, 48 were

**Table 1** Frequency of lymphomas and lymphoma subgroups by country

| | Person—years | Total | | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Lymphomas | NHL | HL | Lymphomas | NHL | HL | Lymphomas | NHL | HL |
| Italy | 263,746 | 80 | 77 | 3 | 27 | 26 | 1 | 53 | 51 | 2 |
| Spain | 267,545 | 67 | 58 | 9 | 32 | 25 | 7 | 35 | 33 | 2 |
| UK | 405,536 | 134 | 128 | 6 | 63 | 61 | 2 | 71 | 67 | 4 |
| Netherlands | 232,151 | 67 | 65 | 2 | 7 | 6 | 1 | 60 | 59 | 1 |
| Greece | 94,831 | 14 | 13 | 1 | 9 | 9 | 0 | 5 | 4 | 1 |
| Germany | 289,082 | 73 | 68 | 5 | 42 | 41 | 1 | 31 | 27 | 4 |
| Sweden | 380,208 | 193 | 183 | 10 | 109 | 102 | 7 | 84 | 81 | 2 |
| Denmark | 369,047 | 207 | 196 | 11 | 125 | 117 | 8 | 82 | 79 | 2 |
| Norway | 108,288 | 14 | 13 | 1 | – | – | – | 14 | 13 | 1 |
| Total | 2,410,434 | 849 | 801 | 48 | 414 | 387 | 27 | 435 | 414 | 21 |

| | NHL subgroups | | | B-NHL subgroups | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | B-NHL | T-NHL | NHL nos | DLBCL | FL | BCLL | MM | Other | B NOS |
| Italy | 70 | 6 | 1 | 12 | 13 | 9 | 18 | 14 | 4 |
| Spain | 53 | 5 | 0 | 12 | 9 | 13 | 13 | 5 | 1 |
| UK | 111 | 4 | 15 | 13 | 15 | 20 | 35 | 8 | 20 |
| Netherlands | 60 | 3 | 2 | 11 | 12 | 9 | 16 | 2 | 10 |
| Greece | 12 | 1 | 0 | 3 | 2 | 2 | 3 | 1 | 1 |
| Germany | 59 | 4 | 5 | 9 | 9 | 5 | 24 | 5 | 7 |
| Sweden | 155 | 2 | 26 | 4 | 4 | 20 | 54 | 9 | 64 |
| Denmark | 181 | 6 | 9 | 42 | 20 | 52 | 34 | 15 | 18 |
| Norway | 12 | 0 | 1 | 0 | 0 | 0 | 2 | 0 | 10 |
| Total | 711 | 31 | 59 | 106 | 84 | 130 | 199 | 59 | 135 |

HL = Hodgkin lymphoma; NHL = Non-Hodgkin lymphoma nos; DLBCL = Diffuse large B-cell lymphoma (incl. Burkitt), FL = Follicular lymphoma (all grades), BCLL = B-cell chronic lymphatic leukemia (incl. SLL, PLL), MM = Multiple myeloma/plasmacytoma

Other = other specified subgroups [BALL (B-cell acute lymphatic leukemia (incl. ALL)], LPL (Lymphoplasmocytic lymphoma/Waldenstroem disease), ML (Marginal zone B-cell lymphoma), BO (B-cell lymphoma, other)]

HL (Table 1). The most frequent subentities were MM ($n$ = 199), BCLL ($n$ = 130), and DLBCL ($n$ = 106). Fifty-nine NHL cases and 135 B-cell lymphomas could not be further specified.

In women, higher education was related to higher vegetable consumption (Table 2). Especially women with a high fruit or vegetable consumption were more likely to be never smokers then women with a low intake. Interestingly, men in the highest quartile of fruit consumption tended to have a higher ethanol intake than men in the lowest quartile. Average fruit and vegetable consumption by EPIC-wide quartiles is shown in Table 3.

## Overall lymphoma risk

There was no statistically significant association between total fruit and vegetable consumption and lymphoma risk (HR = 0.95; 95% CI 0.78–1.15 comparing highest with lowest quartile). Also, neither total fruit nor total vegetable consumption were associated with lymphoma risk (Table 4). These associations did not change materially after excluding the first two years of follow-up (fruit consumption: HR = 1.01; 95% CI 0.77–1.31 comparing highest with lowest quartile; vegetable consumption HR = 0.94; 95% CI 0.70–1.25). Besides an effect for leafy vegetables, there was also no statistically significant association of fruit or vegetable subgroups with lymphoma risk (Table 4). However, participants with the highest intake of leafy vegetables had a non-significantly 27% higher risk of lymphomas than participants with the lowest consumption (Table 4). This effect was attenuated after excluding cases that occurred in the first two years of follow-up (HR = 1.19; 95% CI 0.86–1.63 comparing highest with lowest quartile). No effect modification of the association between fruit and vegetable consumption and the risk of lymphomas by sex and cigarette smoking were observed (data not shown). Also, there was no statistically significant

**Table 2** Baseline characteristics of EPIC study participants by vegetable' and fruit consumption

| | Vegetable consumption | | Fruit consumption | |
|---|---|---|---|---|
| | Lowest quartile | Highest quartile | Lowest quartile | Highest quartile |
| *Males* | | | | |
| Age (years), median (IQR[a]) | 52.0 (44.5–59.3) | 52.6 (44.9–60.7) | 52.4 (45.6–58.8) | 53.1 (46.1–59.6) |
| BMI (kg/m$^2$), median (IQR) | 26.0 (23.8–28.3) | 26.8 (24.4–29.3) | 25.9 (23.8–28.3) | 26.1 (24.0–29.3) |
| Ethanol intake (g/d), median (IQR) | 10.8 (3.3–26.4) | 12.7 (3.8–30.1) | 14.8 (5.0–34.7) | 12.4 (3.9–27.2) |
| Education | | | | |
| Primary school completed (%) | 31.3 | 27.6 | 28.8 | 28.8 |
| University degree (%) | 23.1 | 25.3 | 27.1 | 21.6 |
| *Smoking status* | | | | |
| Never (%) | 29.9 | 30.7 | 27.7 | 30.0 |
| Former (%) | 32.0 | 36.2 | 32.2 | 36.4 |
| Current (%) | 27.1 | 24.4 | 29.9 | 23.0 |
| Other smoking[b] (%) | 11.0 | 8.8 | 10.2 | 10.7 |
| *Females* | | | | |
| Age (years), median (IQR) | 50.5 (43.6–57.1) | 50.7 (42.0–58.4) | 49.5 (42.2–55.2) | 51.7 (44.2–58.7) |
| BMI (kg/m$^2$), median (IQR) | 24.4 (22.1–27.3) | 25.2 (22.5–28.7) | 24.1 (21.8–27.1) | 25.4 (22.8–28.8) |
| Ethanol intake (g/d), median (IQR) | 2.3 (0.4–8.1) | 2.50 (0.4–9.2) | 3.6 (0.8–11.0) | 1.9 (0.2–8.0) |
| *Education* | | | | |
| Primary school completed (%) | 29.5 | 22.9 | 25.7 | 26.5 |
| University degree (%) | 15.1 | 22.6 | 17.5 | 18.7 |
| *Smoking status* | | | | |
| Never (%) | 44.4 | 59.0 | 40.9 | 57.1 |
| Former (%) | 21.9 | 21.3 | 22.1 | 20.6 |
| Current (%) | 27.0 | 15.7 | 33.2 | 15.1 |
| Other smoking[b] (%) | 6.7 | 3.9 | 3.9 | 7.3 |

[a] IQR = interquartile range

[b] cigar or pipe smokers, occasional smokers

heterogeneity in the association between fruit and vegetable consumption and the risk of lymphomas was observed between countries (data not shown).

## Risk of single lymphoma entities

We did not observe a relationship of fruit and vegetable consumption with the risk of HL or T-NHL, but an increased risk of B-NHL with increasing consumption of leafy vegetables (Table 4). The association of leafy vegetable intake with risk of B-NHL was attenuated after excluding the first two years of follow-up (HR = 1.29, 95% CI 0.91–1.82 comparing highest with lowest quartile). Among the considered B-NHL entities, BCLL and FL were most strongly associated with leafy vegetable intake, without reaching, however, statistical significance (Table 4). We also noted a tendency for an elevated risk of BCLL and FL for total fruit intake.

A decreased risk was observed for DLBCL and MM. The risk of DLBCL declined with increasing intake of total vegetables (Table 4), onions and garlic (Table 4), and grain and pod vegetables (HR = 0.40, 95% CI 0.19–0.86 comparing highest with lowest quartile). The association between total vegetable consumption and risk of DLBCL was slightly stronger after excluding the first two years of follow-up (HR = 0.41; 95% CI 0.18–0.97 comparing highest with lowest quartile). The risk of MM decreased with increasing fruit consumption (Table 4). This inverse association was strongest for grape consumption (HR = 0.49, 95% CI 0.27–0.90 comparing highest with lowest quartile).

As already observed in the categorical model, total fruit and vegetable consumption were not associated with lymphoma risk in the continuous model (per 100 g intake: HR = 1.02, 95% CI 0.95–1.09; predicted intake). Although vegetable consumption was inversely related to the risk of DLBCL, the association was not statistically significant in the continuous model (p-trend = 0.09, predicted intake; Table 5). The intake of leafy vegetables tended to be positively associated with BNHL, BCLL, and MM, but none of these associations were statistically significant (Table 5).

**Table 3** Mean vegetable and fruit intake within each quartile of intake, estimated from 24-hour recall

| | | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
|---|---|---|---|---|---|
| Total vegetables (g/day) | Range[a] | <109 | 109–174 | 175–275 | >275 |
| | Mean[b] | 113.4 | 147.0 | 182.2 | 240.5 |
| Leafy vegetables (g/day) | Range | <5 | 5–16 | 17–40 | >40 |
| | Mean | 7.0 | 13.8 | 22.4 | 41.4 |
| Fruiting vegetables (g/day) | Range | <27 | 27–52 | 53–90 | >90 |
| | Mean | 38.4 | 57.5 | 76.5 | 121.0 |
| Cabbages (g/day) | Range | <4 | 4–16 | 17–35 | >35 |
| | Mean | 10.6 | 16.5 | 21.7 | 27.7 |
| Onion and garlic (g/day) | Range | <3 | 3–5 | 6–17 | >17 |
| | Mean | 6.42 | 8.8 | 12.2 | 20.2 |
| Total fruits (g/day) | Range | <105 | 105–193 | 194–319 | >319 |
| | Mean | 95.9 | 169.4 | 243.0 | 335.4 |
| Citrus fruits (g/day) | Range | <8 | 8–28 | 29–71 | >71 |
| | Mean | 19.6 | 22.0 | 46.4 | 85.5 |
| Hard fruits (g/day) | Range | <17 | 17–55 | 56–110 | >110 |
| | Mean | 35.4 | 57.4 | 88.4 | 154.5 |

[a] based on FFQ

[b] based on 24-hour diet recalls

Overall, using predicted instead of observed consumption data did not appreciably change the risk estimates.

## Discussion

With few exceptions, there was no association between fruit and vegetable consumption and the risk of lymphomas in this large prospective cohort study. The risk of DLBCL tended to be lower in participants with a high intake of total vegetables and of onions and garlic, and the risk of MM was lower in participants with high fruit consumption. Participants who consumed high amounts of leafy vegetables had a non-statistically significantly higher lymphoma risk than participants with a low consumption of leafy vegetables. In particular, high leafy vegetable intake was related to a higher risk of B-cell lymphomas.

### Vegetable consumption and lymphoma risk

Our overall result of no association between fruit and vegetable consumption and NHL contrasts with some, but not all, previous studies. Among the cohort studies, the Nurses Health Study showed an inverse association with NHL, whereas the Iowa Women's Health Study did not [18]. In the Nurses Health Study, the decreased risk was related to consumption of vegetables in general and especially cruciferous vegetables, but not green leafy or yellow/orange vegetables [19]. Seven of twelve case–control studies observed inverse, although not always statistically significant associations between vegetable, especially green vegetable, consumption and the risk of NHL [6, 7, 10, 11, 14, 16, 17]. while other reported increased lymphoma risks for subgroups of vegetables [8, 13].

In the EPIC cohort, high consumption of leafy vegetables was related to a higher risk of lymphomas, especially B-cell lymphomas. Leafy vegetables may contain high amounts of nitrate, especially if they grew in green houses. The impact of nitrate intake, e.g., from drinking water, on cancer risk is inconclusive [28], but nitrate is a precursor in the formation of N-nitroso compounds, which may increase the risk of cancer [29, 30]. Vitamin C has been identified as an effective inhibitor of endogenous synthesis of N-nitroso compounds [31]. However, when we adjusted for vitamin C intake in our analysis, the risk estimates were not attenuated appreciably (data not shown). We cannot exclude chance as an explanation for our findings, especially because the association of leafy green vegetable intake and overall lymphoma risk was attenuated after excluding the first two years of follow-up. In contrast to our observation, NHL risk was not elevated among men or women who consumed high amounts of vegetables that may contain high levels of nitrate [10] or who had a high intake of dietary nitrate [32].

### Fruit consumption and lymphoma risk

Neither total fruit consumption nor the consumption of fruit subgroups such as citrus fruits or hard fruits (apples

**Table 4** Multivariate hazard ratios (HR) and 95% confidence intervals (CI) based on quartiles of intakes of fruits and vegetables for all lymphomas and lymphoma entities

| Quartiles[a] | All lymphomas | | HL | | TNHL | | BNHL | | DLBCL | | FL | | BCLL | | MM | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $N_{cases}$ | HR[b] (95% CI) | $N_{cases}$ | HR (95% CI) | $N_{cases}$ | HR (95% CI) | $N_{cases}$ | HR (95% CI) | $N_{cases}$ | HR (95% CI) | $N_{cases}$ | HR (95% CI) | $N_{cases}$ | HR (95% CI) | $N_{cases}$ | HR (95% CI) |
| *Total vegetables* | | | | | | | | | | | | | | | | |
| 1 | 258 | 1.00 (ref.) | 14 | 1.00 (ref.) | 10 | 1.00 (ref.) | 212 | 1.00 (ref.) | 34 | 1.00 (ref.) | 19 | 1.00 (ref.) | 27 | 1.00 (ref.) | 71 | 1.00 (ref.) |
| 2 | 252 | 1.11 | 13 | 1.30 | 10 | 0.89 | 215 | 1.12 | 33 | 0.96 | 29 | 1.36 | 39 | 1.52 | 50 | 0.87 |
| 3 | 192 | 0.95 | 9 | 1.00 | 6 | 0.51 | 165 | 0.97 | 25 | 0.74 | 19 | 1.01 | 37 | 1.46 | 46 | 0.97 |
| 4 | 147 | 1.00 (0.78–1.28) | 12 | 1.60 (0.60–4.24) | 5 | 0.40 (0.11–1.51) | 121 | 1.01 (0.77–1.32) | 14 | 0.49 (0.23–1.02) | 17 | 1.19 (0.54–2.63) | 27 | 1.60 (0.86–2.96) | 32 | 0.93 (0.56–1.57) |
| p-trend | | 0.72 | | 0.48 | | 0.12 | | 0.81 | | 0.05 | | 0.90 | | 0.16 | | 0.85 |
| *Leafy vegetables* | | | | | | | | | | | | | | | | |
| 1 | 237 | 1.00 (ref.) | 12 | 1.00 (ref.) | 11 | 1.00 (ref.) | 193 | 1.00 (ref.) | 29 | 1.00 (ref.) | 16 | 1.00 (ref.) | 31 | 1.00 (ref.) | 61 | 1.00 (ref.) |
| 2 | 261 | 1.19 | 15 | 1.34 | 7 | 0.44 | 219 | 1.25[c] | 35 | 1.16 | 26 | 1.29 | 40 | 1.43 | 56 | 0.95 |
| 3 | 224 | 1.12 | 11 | 1.10 | 5 | 0.26 | 194 | 1.19 | 26 | 0.77 | 25 | 1.24 | 35 | 1.31 | 56 | 1.17 |
| 4 | 127 | 1.27 (0.96–1.67) | 10 | 1.18 (0.37–3.82) | 8 | 0.49 (0.13–1.80) | 107 | 1.38 (1.03–1.86) | 16 | 0.74 (0.34–1.63) | 17 | 1.55 (0.65–3.67) | 24 | 1.94 (0.98–3.82) | 26 | 1.23 (0.69–2.17) |
| p-trend | | 0.13 | | 0.84 | | 0.13 | | 0.048 | | 0.29 | | 0.39 | | 0.10 | | 0.36 |
| *Fruiting vegetables* | | | | | | | | | | | | | | | | |
| 1 | 234 | 1.00 (ref.) | 12 | 1.00 (ref.) | 7 | 1.00 (ref.) | 191 | 1.00 (ref.) | 32 | 1.00 (ref.) | 17 | 1.00 (ref.) | 33 | 1.00 (ref.) | 57 | 1.00 (ref.) |
| 2 | 218 | 0.84 | 10 | 0.88 | 8 | 0.75 | 191 | 0.89 | 26 | 0.64 | 31 | 1.27 | 25 | 0.64 | 49 | 0.84 |
| 3 | 240 | 1.18 | 16 | 1.41 | 8 | 0.75 | 198 | 1.02 | 30 | 0.80 | 19 | 0.84 | 41 | 1.14 | 60 | 1.18 |
| 4 | 157 | 0.89 (0.54–1.47) | 10 | 0.92 (0.34–2.49) | 8 | 0.73 (0.23–2.37) | 133 | 0.90 (0.70–1.16) | 18 | 0.56 (0.28–1.10) | 17 | 0.95 (0.44–2.06) | 31 | 1.20 (0.69–2.10) | 33 | 0.89 (0.54–1.47) |
| p-trend | | 0.62 | | 0.81 | | 0.63 | | 0.74 | | 0.16 | | 0.57 | | 0.22 | | 0.85 |
| *Cabbages* | | | | | | | | | | | | | | | | |
| 1 | 253 | 1.00 (ref.) | 19 | 1.00 (ref.) | 10 | 1.00 (ref.) | 200 | 1.00 (ref.) | 26 | 1.00 (ref.) | 20 | 1.00 (ref.) | 38 | 1.00 (ref.) | 57 | 1.00 (ref.) |
| 2 | 215 | 0.97 | 9 | 0.57 | 14 | 1.40 | 181 | 1.02 | 34 | 0.99 | 23 | 1.24 | 31 | 0.70 | 50 | 1.16 |
| 3 | 198 | 1.06 | 6 | 0.61 | 5 | 0.47 | 176 | 1.17 | 31 | 1.15 | 20 | 1.26 | 34 | 0.88 | 49 | 1.38 |
| 4 | 183 | 1.10 (0.85–1.43) | 14 | 2.31 (0.94–5.65) | 2 | 0.11 (0.02–0.74) | 156 | 1.21 (0.91–1.60) | 15 | 0.75 (0.32–1.75) | 21 | 1.76 (0.72–4.31) | 27 | 0.88 (0.46–1.70) | 43 | 1.18 (0.68–2.07) |
| p-trend | | 0.37 | | 0.15 | | 0.02 | | 0.12 | | 0.80 | | 0.25 | | 0.90 | | 0.37 |
| *Onions and garlic* | | | | | | | | | | | | | | | | |
| 1 | 215 | 1.00 (ref.) | 5 | 1.00 (ref.) | 5 | 1.00 (ref.) | 184 | 1.00 (ref.) | 21 | 1.00 (ref.) | 17 | 1.00 (ref.) | 19 | 1.00 (ref.) | 62 | 1.00 (ref.) |
| 2 | 168 | 0.84 | 13 | 2.65 | 7 | 1.11 | 132 | 0.75[c] | 20 | 0.59 | 15 | 0.70 | 21 | 1.16 | 37 | 0.65 |
| 3 | 229 | 0.81 | 14 | 1.98 | 10 | 1.05 | 196 | 0.78[c] | 31 | 0.43[c] | 25 | 0.92 | 45 | 1.28 | 48 | 0.78 |
| 4 | 237 | 0.90 (0.70–1.16) | 16 | 2.19 (0.61–7.84) | 9 | 0.73 (0.18–2.99) | 201 | 0.88 (0.67–1.16) | 34 | 0.39 (0.18–0.81) | 27 | 1.01 (0.45–2.25) | 45 | 1.26 (0.62–2.54) | 52 | 1.12 (0.67–1.89) |
| p-trend | | 0.39 | | 0.40 | | 0.65 | | 0.39 | | 0.02 | | 0.86 | | 0.56 | | 0.83 |

**Table 4** continued

| Quartiles[a] | All lymphomas | | HL | | TNHL | | BNHL | | DLBCL | | FL | | BCLL | | MM | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $N_{cases}$ | HR[b] (95% CI) | $N_{cases}$ | HR (95% CI) | $N_{cases}$ | HR (95% CI) | $N_{cases}$ | HR (95% CI) | $N_{cases}$ | HR (95% CI) | $N_{cases}$ | HR (95% CI) | $N_{cases}$ | HR (95% CI) | $N_{cases}$ | HR (95% CI) |
| *Total fruits* | | | | | | | | | | | | | | | | |
| 1 | 233 | 1.00 (ref.) | 14 | 1.00 (ref.) | 12 | 1.00 (ref.) | 192 | 1.00 (ref.) | 26 | 1.00 (ref.) | 17 | 1.00 (ref.) | 35 | 1.00 (ref.) | 47 | 1.00 (ref.) |
| 2 | 229 | 1.18 | 10 | 1.58 | 9 | 1.25 | 195 | 1.20 | 37 | 1.23 | 26 | 1.70 | 43 | 1.34 | 58 | 0.97 |
| 3 | 175 | 1.14 | 14 | 1.38 | 3 | 1.03 | 147 | 1.09 | 20 | 1.24 | 19 | 1.29 | 24 | 1.54 | 42 | 0.64[c] |
| 4 | 212 | 1.06 (0.84–1.34) | 10 | 0.87 (0.31–2.42) | 7 | 1.59 (0.48–5.23) | 179 | 1.04 (0.81–1.33) | 23 | 0.83 (0.43–1.62) | 22 | 1.43 (0.68–3.02) | 28 | 1.61 (0.91–2.85) | 52 | 0.60 (0.37–0.98) |
| p-trend | | 0.63 | | 0.93 | | 0.52 | | 0.93 | | 0.69 | | 0.58 | | 0.09 | | 0.01 |
| *Citrus fruits* | | | | | | | | | | | | | | | | |
| 1 | 201 | 1.00 (ref.) | 11 | 1.00 (ref.) | 8 | 1.00 (ref.) | 168 | 1.00 (ref.) | 27 | 1.00 (ref.) | 21 | 1.00 (ref.) | 29 | 1.00 (ref.) | 51 | 1.00 (ref.) |
| 2 | 245 | 1.10 | 14 | 1.44 | 10 | 1.07 | 205 | 1.08 | 27 | 0.96 | 16 | 0.96 | 37 | 1.10 | 65 | 1.12 |
| 3 | 217 | 1.04 | 9 | 1.12 | 6 | 0.51 | 190 | 1.06 | 33 | 1.32 | 28 | 1.32 | 29 | 0.99 | 41 | 0.74 |
| 4 | 186 | 0.97 (0.78–1.21) | 14 | 1.85 (0.79–4.37) | 7 | 0.55 (0.18–1.70) | 150 | 0.92 (0.73–1.17) | 19 | 0.66 (0.34–1.25) | 19 | 0.66 (0.34–1.25) | 35 | 1.33 (0.79–2.26) | 42 | 0.81 (0.52–1.26) |
| p-trend | | 0.72 | | 0.24 | | 0.18 | | 0.57 | | 0.44 | | 0.81 | | 0.37 | | 0.15 |
| *Hard fruits* | | | | | | | | | | | | | | | | |
| 1 | 187 | 1.00 (ref.) | 12 | 1.00 (ref.) | 8 | 1.00 (ref.) | 151 | 1.00 (ref.) | 18 | 1.00 (ref.) | 17 | 1.00 (ref.) | 24 | 1.00 (ref.) | 52 | 1.00 (ref.) |
| 2 | 211 | 1.11 | 13 | 1.63 | 7 | 0.73 | 180 | 1.15 | 31 | 2.07 | 26 | 1.57 | 26 | 1.08 | 49 | 0.89 |
| 3 | 217 | 1.05 | 10 | 1.33 | 7 | 0.65 | 189 | 1.07 | 29 | 1.51 | 24 | 1.23 | 35 | 1.16 | 48 | 0.85 |
| 4 | 234 | 1.06 (0.86–1.31) | 13 | 1.49 (0.62–3.59) | 9 | 0.68 (0.24–1.96) | 193 | 1.04 (0.83–1.32) | 28 | 1.25 (0.65–2.39) | 17 | 0.80 (0.38–1.68) | 45 | 1.41 (0.83–2.41) | 50 | 0.84 (0.55–1.29) |
| p-trend | | 0.74 | | 0.47 | | 0.49 | | 0.94 | | 0.94 | | 0.34 | | 0.18 | | 0.44 |

[a] The quartile ranges are the same as those reported in Table 3

[b] All results are adjusted for tobacco smoking, ethanol intake at baseline, energy intake, and education

[c] Statistically significant association

**Table 5** Multivariate hazard ratios (HR) and 95% confidence intervals (CI) based on calibrated and observed intakes of fruits and vegetables for all lymphomas and lymphoma entities

| | | | All lymphomas HR[a] (95% CI) | HL HR (95% CI) | TNHL HR (95% CI) | BNHL HR (95% CI) | DLBCL HR (95% CI) | FL HR (95% CI) | BCLL HR (95% CI) | MM HR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| Total | Per 100 g | Observed | 0.98 (0.92, 1.05) | 1.08 (0.86, 1.36) | 0.66 (0.43–1.01) | 0.99 (0.92 –1.07) | 0.84 (0.68, 1.04) | 1.07 (0.87–1.31) | 1.05 (0.90–1.23) | 1.03 (0.90–1.18) |
| vegetables | Per 100 g | Predicted | 0.99 (0.81, 1.19) | 1.37 (0.73, 2.58) | 0.42 (0.14–1.28) | 0.99 (0.80–1.22) | 0.62 (0.35, 1.08) | 1.45 (0.85–2.46) | 1.11 (0.71–1.74) | 1.12 (0.75–1.68) |
| Leafy | Per 10 g | Observed | 1.01 (0.99, 1.04) | 1.00 (0.92, 1.07) | 0.92 (0.78–1.06) | 1.02 (0.99–1.05) | 0.94 (0.86, 1.03) | 1.01 (0.93–1.09) | 1.05 (1.00–1.11) | 1.04 (0.98–1.10) |
| vegetables | Per 10 g | Predicted | 1.03 (0.94, 1.12) | 0.98 (0.73, 1.30) | 0.72 (0.49–1.07) | 1.07 (0.97–1.18) | 0.90 (0.70, 1.17) | 1.03 (0.78–1.35) | 1.19 (0.99–1.44) | 1.09 (0.91–1.32) |
| Fruiting | Per 10 g | Observed | 0.99 (0.98, 1.01) | 0.99 (0.94, 1.05) | 0.95 (0.87–1.03) | 0.99 (0.98–1.01) | 0.97 (0.93, 1.02) | 1.00 (0.96–1.05) | 1.02 (0.98–1.05) | 0.99 (0.96–1.03) |
| vegetables | Per 10 g | Predicted | 1.00 (0.96, 1.03) | 1.01 (0.88, 1.16) | 0.93 (0.77–1.13) | 1.00 (0.96–1.04) | 0.94 (0.85, 1.04) | 1.04 (0.94–1.15) | 1.03 (0.95–1.12) | 1.02 (0.95–1.09) |
| Cabbages | Per 10 g | Observed | 1.01 (0.99, 1.03) | 1.04 (0.94, 1.15) | 0.70 (0.52–0.95) | 1.02 (0.99–1.04) | 0.97 (0.88, 1.06) | 0.99 (0.90–1.08) | 1.01 (0.96–1.07) | 1.04 (1.00–1.08) |
| | Per 10 g | Predicted | 1.04 (0.94, 1.14) | 1.08 (0.71, 1.65) | 0.49 (0.23–1.05) | 1.07 (0.97–1.18) | 0.90 (0.66, 1.23) | 0.85 (0.60–1.22) | 1.11 (0.90–1.36) | 1.11 (0.93–1.33) |
| Onion, garlic | Per 10 g | Observed | 1.01 (0.96, 1.07) | 1.06 (0.87, 1.29) | 0.83 (0.60–1.15) | 1.02 (0.96 1.09) | 0.97 (0.83, 1.13) | 1.13 (1.01–1.27) | 0.97 (0.84–1.12) | 1.08 (0.97–1.21) |
| | Per 10 g | Predicted | 0.99 (0.79, 1.25) | 0.78 (0.34, 1.80) | 0.76 (0.28–2.09) | 1.07 (0.83–1.34) | 0.74 (0.40, 1.36) | 1.55 (0.97–2.45) | 1.05 (0.60–1.81) | 1.21 (0.75–1.96) |
| Total fruits | Per 100 g | Observed | 1.02 (0.97, 1.07) | 0.96 (0.78, 1.19) | 1.03 (0.84–1.26) | 1.01 (0.96–1.07) | 1.03 (0.92, 1.17) | 1.06 (0.92–1.22) | 1.07 (0.96–1.20) | 0.93 (0.83–1.03) |
| | Per 100 g | Predicted | 1.04 (0.96, 1.13) | 0.96 (0.67, 1.38) | 1.04 (0.70–1.54) | 1.03 (0.94–1.13) | 1.03 (0.82, 1.29) | 1.10 (0.86–1.41) | 1.18 (0.99–1.41) | 0.86 (0.70–1.05) |
| Citrus fruits | Per 10 g | Observed | 1.00 (0.99, 1.02) | 1.00 (0.95, 1.05) | 1.00 (0.96–1.05) | 1.00 (0.99–1.02) | 1.02 (1.00, 1.04) | 1.01 (0.98–1.05) | 1.02 (0.99–1.05) | 0.97 (0.94–1.00) |
| | Per 10 g | Predicted | 1.00 (0.98, 1.02) | 0.99 (0.90, 1.09) | 1.01 (0.92–1.10) | 1.00 (0.97–1.02) | 1.00 (0.95, 1.06) | 1.03 (0.98–1.09) | 1.03 (0.99–1.08) | 0.93 (0.88–0.99) |
| Hard fruits | Per 100 g | Observed | 1.00 (0.92, 1.09) | 1.21 (0.89, 1.66) | 1.14 (0.80–1.63) | 0.98 (0.90–1.08) | 0.95 (0.76–1.19) | 0.97 (0.73–1.28) | 1.10 (0.91–1.32) | 0.90 (0.74–1.10) |
| | Per 100 g | Predicted | 1.00 (0.87, 1.15) | 1.33 (0.80, 2.21) | 1.16 (0.61–2.21) | 0.97 (0.83–1.13) | 0.92 (0.63, 1.33) | 0.97 (0.61–1.55) | 1.13 (0.83–1.54) | 0.75 (0.52–1.06) |

[a] All results are adjusted for tobacco smoking, ethanol intake at baseline, energy intake, and education

and pears), which were the most commonly consumed fruits, were associated with risk of NHL in our analysis. Fruit consumption was inversely associated with the risk of NHL in the Iowa Women's Health Study [18], but not in the Nurses Health Study [19]. Several case–control studies reported inverse associations of fruit consumption with risk of NHL that were restricted to men [10], women [6, 13], or certain fruit groups [7]. Two case–control studies reported an increased risk of NHL with total fruit [15] or citrus fruit [6] consumption. Four other case–control studies found no association between fruit consumption and risk of NHL [8, 11, 14, 16].

### Entity-specific results

In four studies [9, 12, 14, 15] no association between fruit consumption and risk of MM was observed. However, all besides one [14] noted an inverse relationship of vegetable consumption with risk of MM. Quite in contrast to these results, no association of vegetable consumption and risk of MM was seen in the EPIC cohort, but we noted that participants with a high total fruit consumption and also with a high grape consumption had a lower risk of MM compared with participants in the lowest quintile of intake.

Fruit and vegetable consumption was not consistently associated with risk of NHL-specific entities such as DLBCL, FL, or CLL; effects ranged from decreased to increased risk depending on entity and food group [6, 8]. In the EPIC cohort, we noted several differences by NHL entity. Total vegetable, garlic and onions, as well as grain and pod vegetable consumption were associated with a lower risk of DLBCL but not with any other entity. The risk of DLBCL also tended to be lower in participants who consumed high amounts of fruiting vegetables although the association did not reach statistical significance. Vegetables are rich in antioxidants and other micronutrients, which may decrease cancer risk by effects on DNA damage, immune function, or cell differentiation. However, it is unclear why vegetable consumption might be inversely associated with DLBCL risk but not the risk of other lymphoma subtypes. Since lymphoma entities have different cells of origin, it is not unlikely that they also have different etiologies.

In our analysis, neither fruit nor vegetable consumption was significantly associated with HL risk, although there was a suggestion of a higher risk with increasing cabbage consumption. However, our results are hampered by small numbers due to the fact that HL has two age peaks, the first of which occurs in young adulthood [2]. Since EPIC participants were at least 35-years-old when they joined the study, we were not able to recruit a sufficient number of cases. No statistically significant associations between fruit and vegetable consumption and the risk of HL were reported from two hospital-based case–control studies [14, 15].

### Strengths and limitations

The wide range of fruit and vegetable consumption over the participating centers is a major strength of EPIC. We were also able to take into account potential confounders of the association between fruit and vegetable consumption and the risk of lymphomas. Adjusting by confounders, however, did not appreciably change the results from the age-adjusted models (data not shown). In contrast to some [6, 10, 13] but not all [8] studies, we did not observe effect modification by gender. We compared the association of fruit and vegetable consumption with overall lymphoma and entity-specific risk using calibrated and uncalibrated data. Calibration did not appreciably change the observed associations. Also, the interpretation of the association did not differ whether we used the categorical or the continuous variables.

It has been suggested that inconsistent results between studies might in part be due to varying proportions of lymphoma entities [6] or because of different classification schemes used [5, 33]. We defined entities of lymphomas according to the WHO classification system [23]. However, null effects for fruit and vegetable consumption and the risk of different types of cancer have recently been seen in cohort studies despite inverse associations in previous case–control studies [34–36]. Thus, it is possible that a protective effect of fruit and vegetable consumption has previously been overestimated. Due to the small numbers we had limited power to investigate-specific lymphoma entities. Although some other studies already reported inverse associations between vegetable consumption and the risk of DLBCL, we cannot exclude that, due to the large number of tests done in this study, our results are chance findings. Also, associations might change with longer follow-up or aging of the cohort.

In conclusion, we were unable to confirm the previously observed inverse associations between vegetable consumption and risk of NHL, but we observed an inverse association between vegetable consumption and risk of DLBCL, and fruit consumption and risk of MM. All these observations as well as the positive association between leafy vegetable intake and lymphoma risk need to be confirmed in other studies.

## Appendix

| Entity | ICD-O-3 code |
|---|---|
| Classification of lymphoma subentities based on ICD-O-3 | |
| Hodgkin lymphoma | 9650/3, 9651/3, 9652/3, 9653/3, 9654/3, 9655/3, 9659/3, 9663/3, 9664/3, 9665/3, 9667/3 |
| Non-Hodgkin lymphoma nos | 9590/3 |
| B-cell acute lymphatic leukemia (incl. ALL) | 9727/3, 9835/3, 9728/3, 9836/3 |
| Diffuse large B-cell lymphoma (incl. Burkitt) | 9680/3, 9684/3, 9679/3, 9687/3, 9826/3 |
| Follicular lymphoma (all grades) | 9675/3, 9690/3, 9691/3, 9695/3, 9698/3 |
| B-cell chronic lymphatic leukemia (incl. SLL, PLL) | 9670/3, 9823/3, 9832/3, 9833/3 |
| Lymphoplasmocytic lymphoma/ Waldenstroem disease | 9671/3, 9761/3 |
| Multiple myeloma/plasmacytoma | 9731/3, 9732/3, 9734/3 |
| Marginal zone B-cell lymphoma | 9699/3, 9689/3 |
| B-cell lymphoma, other | 9673/3, 9765/1 |
| T-cell ALL (incl. ALL & adulte T-leucemia) | 9837/3, 9729/3, 9827/3 |
| Mycosis fungoides, Sezary syndrom | 9700/3, 9701/3 |
| Peripheral T-cell lymphoma nos | 9702/3 |
| Cutaneous T-cell lymphoma | 9709/3, 9708/3, 9718/3 |
| Other T-cell lymphomas | 9705/3, 9834/3, 9831/3, 9714/3, 9716/3, 9717/3, 9719/3, 9948/3 |
| Classification of vegetables and fruits | |
| A. Vegetables | |
| Leafy vegetables | Spinach, lettuce (all variants), (swiss) chard, chicory, vine leaf, beet leaves, turnip tops, borage, seaweed, thistle, watercress |
| Fruiting vegetables | Avocado, pepper (sweet, chilli), courgette, tomato, pumpkin, eggplant, artichoke, cucumber/gherkin, french bean, sugar pea, caper, okra |
| Root vegetables | Beetroot, swede, carrot, turnip, parsnip, celeriac, radish, salsify |
| Cabbages | Cabbage (white, red, curly, chinese, sauerkraut, savoy), cauliflower, brussels sprouts, broccoli |
| Mushrooms | All types of mushrooms |
| Grain and pod vegetables | (Sweet) corn, broad bean, pea |
| Onion, garlic | Onion, garlic, shalott |
| Stalk vegetables, sprouts | Blanched celery, leek, fennel, asparagus, sprouts (alfalfa, mungbean, bamboo, other beans) |
| B. Fruits | |
| Citrus fruit | Orange, grapefruit, tangerine, clementine, mandarine, lemon, lime, kumquat |
| Hard fruit | Apple, pear |
| Grape | |
| Stone fruit | Cherry, mirabelle, plum, apricot, peach, nectarine |
| Berries | Strawberry, raspberry, currant, blueberry etc. |
| Citrus fruit juice | Orange juice, grapefruit juice, lemon juice, citrus juice n.s., fresh citrus juice n.s., commercial citrus juice n.s. |

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