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Fruit consumption and the risk of bladder cancer: a pooled analysis by the BLadder cancer Epidemiology and Nutritional Determinants study

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Abbreviations

95% confidence interval = 95% CI
BLadder Cancer Epidemiology and Nutritional Determinants study = BLEND
Carcinoma In Situ = CIS
European Prospective Investigation into Cancer and Nutrition study = EPIC
Food Frequency Questionnaire = FFQ
Hazard Ratio = HR
Melbourne Collaborative Cohort Study = MCCS
Muscle invasive bladder cancer = MIBC
Netherlands Cohort Study = NLCS
Non-muscle invasive bladder cancer = NMIBC
VITamins And Lifestyle cohort study = VITAL
World Cancer Research Fund = WCRF

Novelty and impact statement

Previous studies often lacked adequate numbers with bladder cancer to detect associations between fruit consumption and bladder cancer risk, especially for specific types of fruit and for women. In this large prospective study, we pooled data from 13 cohort studies and found that increasing total fruit consumption may reduce the risk of bladder cancer in women.

Abstract

While the association between fruit consumption and bladder cancer risk has been extensively reported, studies have had inadequate statistical power to investigate associations between types of fruit and bladder cancer risk satisfactorily.

Fruit consumption in relation to bladder cancer risk was investigated by pooling individual data from 13 cohort studies. Cox regression models with attained age as time scale were used to estimate hazard ratios (HRs) for intakes of total fruit and each of citrus fruits, soft fruits, stone fruits, tropical fruits, pome fruits, and fruit products. Analyses were stratified by sex, smoking status, and bladder cancer subtype.

During on average 11.2 years of follow-up, 2836 individuals developed incident bladder cancer. Increasing fruit consumption (by 100 gram/day) was inversely associated with the risk of bladder cancer in women (HR=0.92; 95% CI 0.85-0.99). Although in women the association with fruit consumption was most evident for higher-risk non-muscle invasive bladder cancer (NMIBC) (HR=0.72; 95% CI 0.56-0.92), the test for heterogeneity by bladder cancer subtype was non-significant (p-heterogeneity=0.14). Increasing fruit consumption (by 100 gram/day) was not associated with bladder cancer risk in men (HR=0.99; 95% CI 0.94-1.03), never smokers (HR=0.96; 95% CI 0.88-1.05), former smokers (HR=0.98; 95% CI 0.92-1.05), or current smokers (HR=0.95; 95% CI 0.89-1.01). The consumption of any type of fruit was not found to be associated with bladder cancer risk (p-values>0.05).

This study supports no evidence that the consumption of specific types of fruit reduces the risk of bladder cancer. However, increasing fruit consumption may reduce bladder cancer risk in women.

Introduction

Bladder cancer is the ninth most common cancer worldwide, with almost 550,000 newly diagnosed cases in 2018 (1). Although cigarette smoking is the primary risk factor for bladder cancer, the sex-based difference in bladder cancer incidence is independent of differences in smoking status (2). Dietary factors may contribute to bladder cancer risk considering that many dietary compounds are excreted in urine (3). Fruits contain high levels of phytochemicals, minerals, and antioxidant nutrients, that may hold anti-carcinogenic properties (4). According to a panel of experts of the World Cancer Research Fund (WCRF) Continuous Update Project report 'Diet, nutrition, physical activity and bladder cancer', there is limited evidence from cohort studies that greater consumption of fruits and vegetables may decrease bladder cancer risk (4). Moreover, adherence to the Mediterranean diet, rich in fruits, may decrease the risk of bladder cancer (5). Results from case-control studies have mainly shown inverse associations with fruit consumption, especially for the intake of citrus fruits (6–8). However, recall bias and selection bias may have influenced the reporting of fruit intake in case-control studies and most studies often lacked an adequate number of individuals to detect associations between fruit intake and bladder cancer risk, especially for types of fruits and bladder cancer subtypes. By pooling individual data from multiple cohort studies, the number of bladder cancer cases can be substantially increased with the advantage that the association between fruit intake and bladder cancer risk can be investigated with greater power for different types of fruits and by sex, smoking status, and bladder cancer subtype. In addition, fruit intake categories and covariates can be standardized across studies (unlike in systematic reviews or meta-analyses). The aim of this large-scale study was to build on previous results of the European Prospective Investigation into Cancer and Nutrition (EPIC) studies (9,10) and investigates the association between fruit consumption and bladder cancer risk by pooling data for 535,713 individuals in 13 cohort studies included in the BLadder Cancer Epidemiology and Nutritional Determinants (BLEND) study.

Methods

Study population

The BLEND study is an international consortium that pools individual participant data from international cohort studies and case-control studies. Details of the methodology of the BLEND study have been described elsewhere (11). Briefly, a total of 13 cohort studies had sufficient data to be eligible for inclusion in this study (i.e. method of dietary assessment, geographical region, disease status). About 75% of the study populations originated from centers in Europe including the EPIC studies (12,13) and the Netherlands Cohort Study (NLCS) (14). Other populations originated from Australia (Melbourne Collaborative Cohort Study (MCCS)) (15) and North America (VITamins And Lifestyle cohort study (VITAL)) (16). All studies have been ethically approved and all study participants provided informed consent.

Bladder cancer ascertainment

Each study ascertained incident bladder cancers with International Classification of Diseases (ICD-O-three code C67) using population-based cancer registries, health insurance records, cancer registries, or medical records. Linkages to mortality registries were conducted during the follow-up period of each study. The term bladder cancer is used for all urinary bladder neoplasms. Bladder cancers were classified into non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC). NMIBCs included noninvasive carcinomas confined to the urothelium (stage Ta), carcinomas that invaded the lamina propria of the bladder wall (stage T1), and high grade flat noninvasive carcinomas confined to the urothelium (carcinoma in situ; CIS). MIBCs included carcinomas that invaded into the detrusor muscle (stage T2), carcinomas that invaded into the peri vesical tissue (stage T3), and carcinomas that invaded adjacent tissues and organs (most often the prostate or uterus) (stage T4). With bladder cancer representing a heterogeneous group of tumours, that possibly develop through different but interrelated pathways (17) and could have implications for treatments and outcomes, NMIBCs were further divided into “lower” risk (stage Ta with a low grade (grade 1 or grade 2)) and “higher” risk (stage Ta with grade 3, stage T1, and CIS). Whilst lower-risk NMIBC often occurs from papillary tumours, higher-risk NMIBC and MIBC are more likely to develop from non-papillary tumours (18).

Dietary assessment

For each study, participants were asked to report on their usual fruit consumption during the preceding year before study enrolment. All the studies assessed usual dietary intake with a validated food frequency questionnaire (FFQ). To harmonise data collected from the study specific FFQs and to consider the varying portions sizes between different populations, frequency intakes were converted to grams using the portion sizes described in the FFQ of each study. Where applicable, fruit intakes were converted from weekly, monthly, or yearly intakes, to daily intakes. The consumption of fruits in grams per day was then standardised across studies by making use of the Eurocode 2 food coding system (19). Total fruit intake was computed as the sum of grams of all fruit items or fruit groups (excluding fruit juices) provided by each study. The following types of fruits were defined: citrus fruits, pome fruits, soft fruits, stone fruits, tropical fruits, and fruit products (Table 1).

Statistical analysis

Person-years of follow-up for each participant were calculated from date of study enrolment until the date of a first bladder cancer diagnosis, death, emigration, last known contact, or end of study follow-up, whichever came first. For the NLCS, a nested case-cohort approach was applied, in which the number of person-years at risk was estimated based on a subcohort that was randomly sampled after baseline (14). Total fruit consumption was analysed both as a continuous variable (expressing results per 100 grams per day in usual total fruit consumption), and a categorical variable. For the categorical variable, total fruit consumption was divided into four intake categories: <100 grams of fruit per day (less than approximately one piece of fruit), 100-200 grams of fruit per day (approximately one to two pieces of fruit), 200-300 grams of fruit per day (approximately two to three pieces of fruit), and >300 grams of fruit per day (more than approximately three pieces of fruit), using the lowest intake category as a reference. Fruit types (citrus fruits, soft fruits, stone fruits, tropical fruits, pome fruits, and fruit products) were each analysed as a continuous variable per 25 grams of fruits per day increase and were modelled into quartiles, using the lowest quartile as a reference. Cox proportional hazard models with attained age as time scale were used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) for bladder cancer. The assumption of proportional hazards was examined for the relationship of scaled Schoenfeld residuals with time and appeared to be violated when considering all participants together (20). Based on *a priori* reasons and the violation of the proportional hazard assumption for all participants, analyses were performed for sex, smoking status (never smokers, former smokers, current smokers), and bladder cancer subtype (NMIBC and MIBC, and further classification into lower-risk NMIBC and higher-risk NMIBC); the assumption of proportional hazards was now found to be satisfied in all models. Heterogeneity was calculated by the duplication method for Cox regression as described by Lunn *et al.* (21), using a likelihood ratio test to compare the model with and without interaction terms between total fruit consumption and sex, smoking status, and bladder cancer subtype. Within the regression models, all analyses were stratified by cohort, sex, and age at study enrolment. Adjustment was made for the potential confounders smoking status (current smoker/former smoker/never smoker), pack-years of cigarette smoking (continuous in years), ethnicity (Asian/Black/Caucasian), total vegetable consumption (continuous in gram/day), alcohol intake (continuous in gram/day), and total energy intake (continuous in kcal/day). A sensitivity analysis was performed on pre-defined sex-specific energy intake cut offs (800-4000 kcal/day for women and 1500-6000 kcal/day for men). All statistical analyses were performed using Stata software version 14 and a two-sided p-value of <0.05 was considered statistically significant.

Data Availability

The data that support the findings of this study are not publicly available, but data will be made available upon reasonable request.

Results

Baseline characteristics of the study samples included are presented in Table 2. Of 597,231 potentially eligible participants, 61,327 individuals were excluded from the statistical analyses for having missing data on total fruit consumption (n=28,929), total vegetable consumption (n=173), ethnicity (n=472), pack-years of smoking (n=27,476), or for missing and extreme values (<800 kcal/day and >6000 kcal/day) of total energy intake (n=46,906). In addition, individuals with incident bladder cancers diagnosed within the first two years of study follow-up were excluded (n=191) (Figure 1). During an average of 11.2 years of follow-up, 2836 of the remaining 535,713 participants were diagnosed with an incident bladder cancer. A total of 1135 cases were classified as NMIBC and 706 as MIBC; 995 bladder cancers could not be classified due to missing data on tumour characteristics.

Total fruit

In men, increasing fruit consumption by 100 grams per day was not associated with overall bladder cancer risk (HR=0.99; 95% CI 0.94-1.03) (Table 3), or with any bladder cancer subtype (p-heterogeneity=0.33) (Table 4). The sensitivity analysis on sex-specific cut offs for total energy intake in men per 100 grams of fruit per day increase showed a comparable result (HR=0.99; 95% CI 0.94-1.04). Compared with the lowest category of fruit intake (<100 grams of fruit per day), the highest total fruit intake category (>300 grams of fruit per day) was associated with a lower risk of overall bladder cancer in women (HR=0.75; 95% CI 0.59-0.97) (Table 3). In the continuous analysis for women, increasing total fruit consumption by 100 grams per day was inversely associated with the risk of overall bladder cancer (HR=0.92; 95% CI 0.85-0.99) (Table 3). A similar result for increasing total fruit consumption and bladder cancer risk in women was obtained from the sensitivity analysis when sex-specific cut offs for total energy intake were used (HR=0.92; 95% 0.85-0.99). Although in women the association was stronger for higher-risk NMIBC (HR=0.72; 95% CI 0.56-0.92) than for all NMIBCs combined (HR=0.79; 95% CI 0.67-0.94), the test for heterogeneity by bladder cancer subtype did not reach significance (p-heterogeneity=0.14) (Table 4). In the subgroup analysis on smoking status, the consumption of fruit was not associated with the risk of bladder cancer in never smokers (HR=0.96; 95% CI 0.88-1.05), former smokers (HR=0.98; 95% CI 0.92-1.05), current smokers (HR=0.95; 95% CI 0.89-1.01) (Table 3), or ever smokers (current and former smokers combined) (HR=0.96; 95% CI 0.92-1.01).

Subtypes of fruit

In women, no associations were found between increasing consumption by 25 grams per day of citrus fruits (HR=0.97; 95% CI 0.92-1.03), soft fruits (HR=0.95; 95% CI 0.84-1.09), stone fruits (HR=0.94; 95% CI 0.85-1.03), pome fruits (HR=0.95; 95% CI 0.87-1.03), or fruit products (HR=1.00; 95% CI 0.76-1.32), and overall bladder cancer risk (Table 3). Although for tropical fruit intake an association was found with the risk of overall bladder cancer in women in the categorical analysis (highest quintile vs. lowest quintile HR=0.78; 95% CI 0.62-0.99, p-trend=0.05), the continuous analysis for increasing tropical fruit consumption by 25 grams per day showed no association (HR=0.97; 95% CI 0.91-1.04). In the analysis for men and on smoking status, no associations were found between any specific type of fruit and the risk of overall bladder cancer (p>0.05) (Table 3).

Discussion

In this analysis of pooled data from 13 prospective cohort studies, comprising 2836 individuals with incident bladder cancer, an association was found between increasing total fruit consumption and a decreased risk of bladder cancer in women. No associations were found between fruit consumption and the risk of bladder cancer for men, current smokers, former smokers, or never smokers (9,10). With bladder cancer being a heterogeneous disease, attention has increasingly focused on investigating subtypes of bladder cancer. While in the EPIC study, tumours were defined as non-aggressive urothelial cell carcinomas or aggressive urothelial cell carcinomas (10), the classification of bladder tumours for this BLEND study included lower-risk NMIBC, higher-risk NMIBC and MIBC. However, there were no significant differences between the risk associations for the bladder cancer subtypes in relation to the consumption of fruit using the duplication method for Cox regression as described by Lunn *et al.* (21). The addition of incident bladder cancers from three additional large cohorts (NLCS, MCCS, and VITAL) could explain the novel finding for the inverse association between total fruit consumption and bladder cancer risk for women. Although most prospective studies on bladder cancer risk found no associations with fruit consumption (22–25), the findings for women are in partial agreement with results of the Multiethnic Cohort study (26). Park *et al.* (26) found that only for women, total fruit and citrus fruit consumptions were inversely associated with the risk of bladder cancer (HR=0.54; 95% CI 0.34-0.85 and HR=0.56; 95% CI 0.34-0.90, respectively). Interestingly, the authors showed that there was only a significant association with fruit consumption for women when considering invasive bladder cancer as an endpoint, not non-invasive bladder cancer (26). Results from the Nurses' Health study on lung cancer (a smoking-related cancer as bladder cancer) also showed that especially women with greater intakes of fruit had a reduced risk of cancer (27). It cannot be excluded that the inverse association found for women but not men may be partially explained by differences in hormonal factors (e.g. estrogen) and urination habits between men and women, or by residual confounding by smoking habits, though the inverse association for women in the Multiethnic Cohort study was found after rigorous adjustment for cigarette smoking and reproductive factors (26). Although statistical power was more limited for women compared with men (683 incident bladder cancers in women and 2153 incident bladder cancers in men), especially in the categorical analysis of fruit intake, the number of incident bladder cancers in the continuous analyses for increasing total fruit consumption by 100 grams per day in women had adequate power. All types of fruit showed non-significant associations with the risk of bladder cancer (all $p>0.05$) and therefore the inverse association between fruit consumption and bladder cancer risk in women cannot be attributed to increased consumption of a specific type of fruit.

This study has several strengths, including the large sample size providing statistical power to examine different types of fruits, the possibility to classify risks by sex, smoking status, and bladder cancer subtype, and the inclusion of studies from 12 different countries. Although the use of a calibration method might have reduced between-country heterogeneity in dietary intake, results of both the EPIC study (9) and the Multiethnic Cohort study (26) on fruit consumption and bladder cancer risk indicated that after applying a calibration method (28), there were no substantial differences between their observed findings and their calibrated estimates. Although by making use of the Eurocode 2 Food Coding System (19) the potential for misclassification for the types of fruit is limited, measurement error in the dietary assessment by limitations of the FFQs, including over- and under-reporting of usual fruit consumption, and the inability to investigate dietary changes over time with only one single measurement of fruit at time of study entry, cannot be excluded. However, if changes in dietary intake were made by individuals during follow-up, it would still be questionable whether these changes would have influenced bladder cancer risk in this relatively short period of time. Other limitations of this study were the limited information on covariates that may be associated with the risk of bladder cancer (and that are highly correlated with fruit consumption), such as body mass index, physical activity, and socioeconomic status. However, it has been indicated that these factors may probably account for only a small percentage of bladder cancer cases overall (29,30).

In conclusion, there was no evidence that the consumption of specific types of fruit reduces the risk of bladder cancer. However, increasing consumption of the total amount of fruits may reduce bladder cancer risk in women.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

DISCLAIMER

Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

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Table 1. Classification of types of fruit based on composition

Types of fruit	Composition
Citrus fruits	lemons, oranges, tangerines, grapefruits, pomelos, limes, kumquats
Soft fruits	strawberries, raspberries, white grapes, black grapes, loganberries, blackberries, dewberries, cloudberries, gooseberries, black currants, red currants, white currants, cranberries, bilberries, cowberries, blueberries, elderberries, rowanberries, physalis, mulberries, bearberries, sea buckthorns
Stone fruits	apricots, peaches, nectarines, plums, damsons, mirabelles, greengages, sweet cherries, sour cherries, chickasaws, susinas, sloes, dates, lychees, persimmons, barbados cherries
Pome fruits	apples, pears, quinces, medlars, and loquats
Tropical fruits	bananas, pineapples, kiwi fruits, (water)melons, figs, mangos, pomegranates, passion fruits, cashew fruits, guavas, papayas, rose hips, sapodillas, carambolas, durians, jack fruit, chayotes, rambutans, tamarinds
Fruit products	dried mixed fruits, mixed peels, glace cherries, crystallized pineapple, apple sauce, cranberry sauce
Fruit mixtures	fruit salads, fruit cocktails

Table 2. Baseline characteristics of individuals from the 13 cohort studies included in the pooled analysis

	EPIC Denmark	EPIC France	EPIC Germany	EPIC Greece	EPIC Italy	EPIC The Netherlands	EPIC Norway	EPIC Spain	EPIC Sweden	EPIC United Kingdom	NLCS The Netherlands (case-cohort design)	MCCS Australia	VITAL USA	Total in BLEND study
	No.[a] (%) / (mean (SD))	No.[a] (%) / (mean (SD))	No.[a] (%) / (mean (SD))	No.[a] (%) / (mean (SD))	No.[a] (%) / (mean (SD))	No.[a] (%) / (mean (SD))	No.[a] (%) / (mean (SD))	No.[a] (%) / (mean (SD))	No.[a] (%) / (mean (SD))	No.[a] (%) / (mean (SD))	No.[a] (%) / (mean (SD))	No.[a] (%) / (mean (SD))	No.[a] (%) / (mean (SD))	No.[a] (%) / (mean (SD))
Total participants	56,005 (9)	64,866 (11)	49,457 (8)	25,268 (4)	45,204 (8)	37,102 (6)	33,856 (6)	40,782 (7)	49,328 (8)	75,035 (13)	5632 (1)	38,263 (6)	76,433 (13)	597,231 (100)
Men	26,764 (13)	0	21,551 (11)	10,438 (6)	14,084 (7)	9801 (5)	0	15,439 (8)	22,546 (11)	22,476 (11)	3052 (2)	15,798 (8)	36,453 (18)	198,402 (100)
Women	29,241 (7)	64,866 (16)	27,906 (7)	14,830 (4)	31,120 (8)	27,301 (7)	33,856 (8)	25,343 (6)	26,782 (7)	52,559 (13)	2580 (1)	22,465 (6)	39,980 (10)	398,829 (100)
All incident bladder cancers[b]	391 (11)	31 (<1)	207 (6)	50 (1)	187 (5)	107 (3)	24 (<1)	152 (4)	303 (9)	248 (7)	940 (27)	520 (15)	378 (11)	3538 (100)
Lower-risk NMIBC	87 (17)	17 (3)	79 (16)	-	46 (9)	71 (14)	-	21 (4)	-	0 (<1)	-	188 (37)	-	509 (100)
Higher-risk NMIBC	51 (8)	5 (<1)	35 (5)	-	58 (9)	22 (3)	-	29 (4)	-	1 (<1)	409 (61)	47 (7)	15 (2)	672 (100)
MIBC	44 (5)	5 (<1)	40 (4)	-	20 (2)	23 (2)	-	7 (<1)	-	6 (<1)	443 (47)	232 (24)	121 (13)	941 (100)
Mean age at study entry (yrs)	56.7 (4.4)	52.8 (6.6)	50.6 (8.6)	53.3 (12.6)	50.5 (7.9)	48.9 (12.0)	48.1 (4.3)	49.2 (8.0)	52.0 (10.9)	49.1 (14.4)	62.1 (4.2)	55.0 (8.7)	61.4 (7.5)	52.9 (10.2)
Never smoker	19,624 (7)	45,797 (15)	22,658 (7)	14,060 (4)	20,540 (7)	14,171 (6)	12,057 (4)	22,599 (8)	24,205 (8)	41,948 (14)	1848 (1)	22,057 (7)	35,818 (12)	297,324 (100)
Former smoker	17,070 (10)	13,121 (7)	16,386 (9)	4232 (2)	12,096 (7)	11,572 (7)	10,438 (6)	7207 (4)	13,410 (8)	23,924 (14)	2018 (1)	11,848 (7)	33,648 (18)	176,970 (100)
Current smoker	19,624 (16)	5948 (5)	10,413 (9)	6976 (6)	12,568 (10)	11,359 (9)	11,361 (9)	10,976 (9)	11,713 (10)	9163 (7)	1766 (1)	4358 (4)	6412 (5)	122,324 (100)
Mean total fruit intake (g/day)	179.3 (149)	263.2 (168)	138.8 (100)	358.8 (201)	340.5 (213)	196.4 (137)	156.9 (121)	335.2 (223)	175.9 (130)	250.2 (201)	173.3 (119)	241.0 (150)	93.9 (90)	211.4 (183)

BLEND= BLadder cancer Epidemiology and Nutritional Determinants study, EPIC=The European Prospective Investigation into Cancer and Nutrition study, NLCS=The Netherlands Cohort Study, MCCS=The Melbourne Collaborative Cohort Study, VITAL=The VITamins And Lifestyle cohort, NMIBC=non-muscle invasive bladder cancer, MIBC=muscle invasive bladder cancer

[a] As a result of the exclusion criteria, cohort study size and number of cases included in BLEND may differ from original study-specific publications

[b] For a total of 1416 bladder cancers the histological bladder cancer subtype was not specified

Table 3. Adjusted hazard ratios for all bladder cancers by total fruit consumption and the consumption of specific types of fruit

	Full cohort		Males		Females		Never smokers		Former smokers		Current smokers	
	Cases	HR[a,b] (95% CI)	Cases	HR[a] (95% CI)	Cases	HR[a] (95% CI)	Cases	HR[a] (95% CI)	Cases	HR[a] (95% CI)	Cases	HR[a] (95% CI)
Total fruit												
<100 grams of fruit per day	1044	1.00 (ref)	866	1.00 (ref)	178	1.00 (ref)	169	1.00 (ref)	424	1.00 (ref)	451	1.00 (ref)
100–200 grams of fruit per day	824	0.93 (0.84-1.02)	620	0.95 (0.85-1.06)	204	0.83 (0.68-1.03)	187	1.10 (0.87-1.40)	318	0.85 (0.73-1.00)	319	0.94 (0.81-1.09)
200–300 grams of fruit per day	492	0.92 (0.82-1.04)	341	0.95 (0.83-1.10)	151	0.83 (0.65-1.04)	123	0.96 (0.73-1.26)	215	0.96 (0.80-1.16)	154	0.86 (0.71-1.05)
>300 grams of fruit per day	476	0.90 (0.79-1.02)	326	0.96 (0.83-1.12)	150	0.75 (0.59-0.97)	134	0.93 (0.70-1.23)	197	0.91 (0.74-1.11)	145	0.87 (0.70-1.08)
p for trend		>0.05		>0.05		0.04		>0.05		>0.05		>0.05
Per 100 grams a day	2836	0.97 (0.93-1.01)	2153	0.99 (0.94-1.03)	683	0.92 (0.85-0.99)	613	0.96 (0.88-1.05)	1154	0.98 (0.92-1.05)	1069	0.95 (0.89-1.01)
Citrus fruit												
Q1	773	1.00 (ref)	612	1.00 (ref)	161	1.00 (ref)	129	1.00 (ref)	292	1.00 (ref)	352	1.00 (ref)
Q2	626	0.96 (0.86-1.07)	470	0.97 (0.85-1.09)	156	0.93 (0.74-1.17)	118	0.87 (0.68-1.12)	259	1.03 (0.87-1.23)	249	0.94 (0.80-1.11)
Q3	558	0.97 (0.87-1.08)	393	0.98 (0.86-1.12)	165	0.92 (0.74-1.15)	144	1.10 (0.86-1.41)	198	0.88 (0.73-1.06)	216	0.98 (0.82-1.17)
Q4	608	0.97 (0.87-1.09)	430	1.01 (0.88-1.15)	178	0.88 (0.70-1.11)	142	0.95 (0.76-1.28)	247	1.04 (0.86-1.25)	219	0.91 (0.75-1.09)
p for trend		>0.05		>0.05		>0.05		>0.05		>0.05		>0.05
Per 25 grams a day	2565	1.00 (0.97-1.03)	1905	1.01 (0.97-1.04)	660	0.97 (0.92-1.03)	533	1.02 (0.96-1.09)	996	1.00 (0.96-1.05)	1036	0.98 (0.93-1.02)
Soft fruit												
Q1	523	1.00 (ref)	400	1.00 (ref)	123	1.00 (ref)	100	1.00 (ref)	216	1.00 (ref)	207	1.00 (ref)
Q2	952	1.02 (0.90-1.15)	754	1.04 (0.91-1.20	198	0.94 (0.72-1.23)	199	1.13 (0.86-1.48)	393	1.06 (0.88-1.27)	360	0.95 (0.77-1.16)
Q3	857	0.94 (0.83-1.07)	653	1.00 (0.87-1.15)	204	0.78 (0.60-1.01)	198	1.00 (0.76-1.32)	333	0.90 (0.75-1.10)	326	0.98 (0.80-1.20)
Q4	504	1.00 (0.87-1.14)	346	1.08 (0.92-1.26)	158	0.79 (0.60-1.04)	116	0.86 (0.64-1.16)	212	1.11 (0.90-1.37)	176	1.00 (0.79-1.25)
p for trend		>0.05		>0.05		0.05		>0.05		>0.05		>0.05
Per 25 grams a day	2836	1.00 (0.93-1.08)	2153	1.03 (0.94-1.13)	683	0.95 (0.84-1.09)	613	0.91 (0.78-1.07)	1154	1.09 (0.97-1.22)	1069	0.98 (0.86-1.12)
Stone fruit												
Q1	469	1.00 (ref)	379	1.00 (ref)	90	1.00 (ref)	117	1.00 (ref)	208	1.00 (ref)	144	1.00 (ref)
Q2	620	1.11 (0.97-1.28)	475	1.08 (0.93-1.26)	145	1.26 (0.91-1.75)	136	0.93 (0.70-1.24)	233	1.06 (0.86-1.31)	251	1.39 (1.08-1.79)
Q3	526	1.00 (0.86-1.16)	357	1.00 (0.84-1.19)	169	1.04 (0.75-1.43)	130	0.79 (0.58-1.06)	210	1.03 (0.81-1.30)	186	1.19 (0.92-1.54)
Q4	422	1.01 (0.84-1.20)	280	1.04 (0.85-1.28)	142	0.98 (0.69-1.39)	119	0.82 (0.58-1.15)	165	1.05 (0.79-1.39)	138	1.14 (0.84-1.53)
p for trend		>0.05		>0.05		>0.05		>0.05		>0.05		>0.05
Per 25 grams a day	2037	0.99 (0.94-1.04)	1491	1.02 (0.95-1.08)	546	0.94 (0.85-1.03)	502	0.97 (0.88-1.08)	816	1.00 (0.92-1.09)	719	1.00 (0.91-1.09)

[a] Model stratified by cohort, age at study entry, and sex (where applicable), and adjusted for smoking status and pack-years of cigarette smoking (where applicable), ethnicity, total vegetable consumption, alcohol intake, and total energy intake

[b] The assumption of proportional hazards was violated

Table 3. continued

	Full cohort		Males		Females		Never smokers		Former smokers		Current smokers	
	Cases	HR[a,b] (95% CI)	Cases	HR[a] (95% CI)	Cases	HR[a] (95% CI)	Cases	HR[a] (95% CI)	Cases	HR[a] (95% CI)	Cases	HR[a] (95% CI)
Tropical fruit												
Q1	1053	1.00 (ref)	824	1.00 (ref)	229	1.00 (ref)	189	1.00 (ref)	387	1.00 (ref)	477	1.00 (ref)
Q2	539	0.84 (0.75-0.93)	417	0.87 (0.77-0.99)	122	0.71 (0.56-0.90)	90	0.63 (0.48-0.82)	233	1.01 (0.85-1.20)	213	0.81 (0.68-0.96)
Q3	599	0.90 (0.81-1.01)	453	0.96 (0.84-1.08)	146	0.74 (0.59-0.94)	152	0.83 (0.65-1.06)	245	0.95 (0.80-1.13)	202	0.93 (0.78-1.11)
Q4	645	0.94 (0.83-1.05)	459	0.98 (0.86-1.12)	186	0.78 (0.62-0.99)	179	0.82 (0.64-1.05)	289	1.07 (0.89-1.28)	177	0.87 (0.72-1.06)
p for trend		>0.05		>0.05		0.05		>0.05		>0.05		>0.05
Per 25 grams a day	2836	0.98 (0.95-1.02)	2153	0.99 (0.95-1.03)	683	0.97 (0.91-1.04)	613	0.99 (0.93-1.06)	1154	1.01 (0.96-1.07)	1069	0.93 (0.87-1.00)
Pome fruit												
Q1	393	1.00 (ref)	331	1.00 (ref)	62	1.00 (ref)	52	1.00 (ref)	156	1.00 (ref)	185	1.00 (ref)
Q2	213	0.86 (0.73-1.02)	172	0.87 (0.72-1.05)	41	0.83 (0.56-1.24)	39	0.80 (0.53-1.22)	85	0.74 (0.56-0.96)	89	1.03 (0.80-1.32)
Q3	179	0.83 (0.69-0.99)	139	0.83 (0.68-1.02)	40	0.79 (0.52-1.18)	44	0.82 (0.54-1.23)	86	0.81 (0.62-1.06)	49	0.84 (0.61-1.14)
Q4	286	0.90 (0.77-1.05)	226	0.91 (0.77-1.09)	60	0.83 (0.58-1.20)	61	0.81 (0.55-1.18)	153	0.93 (0.74-1.17)	72	0.78 (0.60-1.03)
p for trend		>0.05		>0.05		>0.05		>0.05		>0.05		>0.05
Per 25 grams a day	1071	0.98 (0.94-1.01)	868	0.98 (0.94-1.02)	203	0.95 (0.87-1.03)	196	0.96 (0.88-1.04)	480	1.00 (0.94-1.05)	395	0.95 (0.89-1.01)
Fruit products												
Q1	345	1.00 (ref)	278	1.00 (ref)	67	1.00 (ref)	56	1.00 (ref)	161	1.00 (ref)	128	1.00 (ref)
Q2	69	0.98 (0.74-1.30)	52	1.05 (0.76-1.45)	17	0.77 (0.43-1.38)	20	0.75 (0.44-1.28)	36	1.05 (0.71-1.55)	13	1.25 (0.65-2.39)
Q3	216	0.95 (0.80-1.12)	174	0.98 (0.81-1.19)	42	0.80 (0.54-1.18)	38	0.82 (0.54-1.25)	107	1.05 (0.82-1.34)	71	0.84 (0.63-1.13)
Q4	441	0.86 (0.74-1.00)	364	0.90 (0.76-1.06)	77	0.71 (0.50-1.00)	82	0.86 (0.60-1.24)	176	0.82 (0.66-1.03)	183	0.88 (0.69-1.12)
p for trend		>0.05		>0.05		>0.05		>0.05		>0.05		>0.05
Per 25 grams a day	1071	0.98 (0.87-1.11)	868	0.97 (0.85-1.12)	203	1.00 (0.76-1.32)	196	1.12 (0.86-1.45)	480	0.85 (0.68-1.06)	395	1.03 (0.85-1.24)

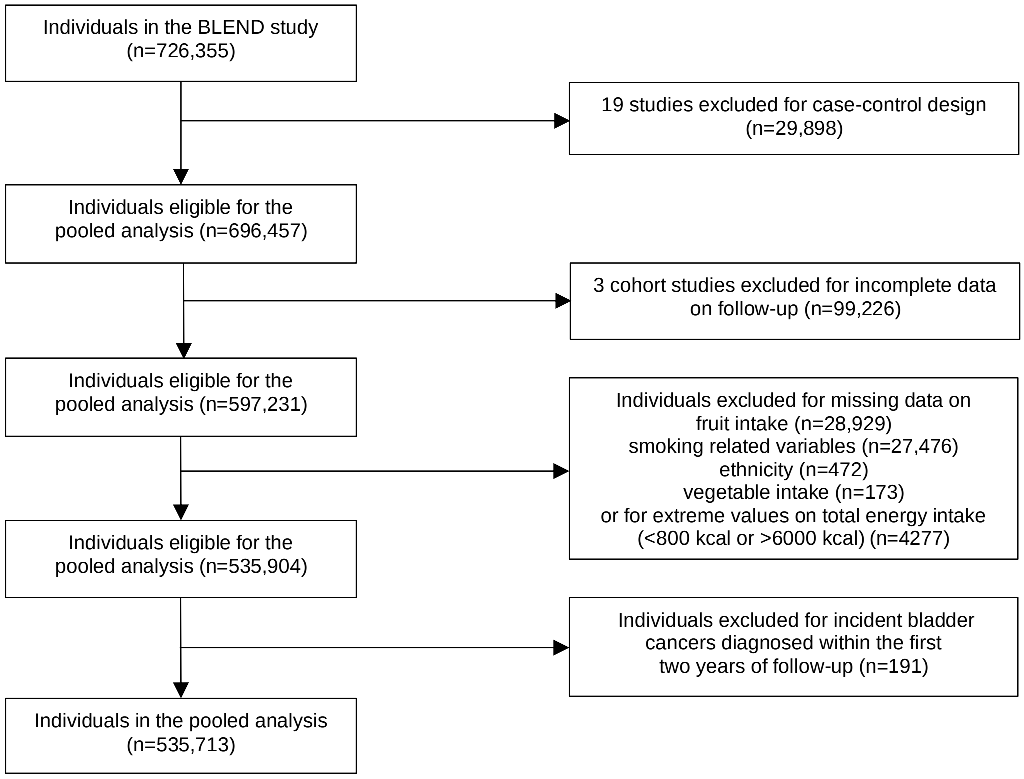
[a] Model stratified by cohort, age at study entry, and sex (where applicable), and adjusted for smoking status and pack-years of cigarette smoking (where applicable), ethnicity, total vegetable consumption, alcohol intake, and total energy intake

[b] The assumption of proportional hazards was violated

Table 4. Adjusted hazard ratios for subtypes of bladder cancer by total fruit consumption

	All NMIBC		Lower-risk NMIBC		Higher-risk NMIBC		MIBC	
	Cases	HR[a] (95% CI)	Cases	HR[a] (95% CI)	Cases	HR[a] (95% CI)	Cases	HR[a] (95% CI)
Total fruit intake in men								
<100 grams of fruit per day	386	1.00 (ref)	80	1.00 (ref)	166	1.00 (ref)	239	1.00 (ref)
100–200 grams of fruit per day	242	0.96 (0.81-1.15)	74	1.00 (0.72-1.39)	152	0.93 (0.74-1.16)	164	0.92 (0.74-1.14)
>200 grams of fruit per day	239	0.92 (0.75-1.12)	92	0.87 (0.61-1.24)	139	0.96 (0.75-1.24)	168	1.03 (0.82-1.30)
p for trend		>0.05		>0.05		>0.05		>0.05
Per 100 grams a day	867	0.96 (0.87-1.06)	246	0.93 (0.78-1.11)	457	0.98 (0.86-1.11)	571	1.01 (0.90-1.14)
Total fruit intake in women								
<100 grams of fruit per day	83	1.00 (ref)	31	1.00 (ref)	33	1.00 (ref)	35	1.00 (ref)
100–200 grams of fruit per day	77	0.75 (0.54-1.04)	39	0.85 (0.53-1.39)	38	0.74 (0.46-1.19)	44	0.91 (0.57-1.45)
>200 grams of fruit per day	108	0.63 (0.45-0.88)	59	0.76 (0.47-1.23)	46	0.52 (0.31-0.85)	56	0.94 (0.59-1.49)
p for trend		0.01		>0.05		0.01		>0.05
Per 100 grams a day	268	0.79 (0.67-0.94)	129	0.87 (0.69-1.11)	117	0.72 (0.56-0.92)	135	0.97 (0.77-1.23)
Total fruit intake in never smokers								
<100 grams of fruit per day	83	1.00 (ref)	16	1.00 (ref)	21	1.00 (ref)	43	1.00 (ref)
100–200 grams of fruit per day	75	1.11 (0.77-1.61)	33	1.22 (0.67-2.25)	36	1.07 (0.62-1.87)	33	0.87 (0.51-1.49)
>200 grams of fruit per day	90	0.80 (0.54-1.19)	50	0.97 (0.53-1.79)	34	0.58 (0.31-1.06)	50	0.99 (0.58-1.69)
p for trend		>0.05		>0.05		>0.05		>0.05
Per 100 grams a day	248	0.88 (0.72-1.06)	99	0.95 (0.71-1.26)	91	0.74 (0.56-1.00)	126	1.01 (0.78-1.32)
Total fruit intake in former smokers								
<100 grams of fruit per day	203	1.00 (ref)	39	1.00 (ref)	72	1.00 (ref)	118	1.00 (ref)
100–200 grams of fruit per day	125	0.85 (0.66-1.10)	37	0.80 (0.51-1.28)	80	0.91 (0.65-1.27)	85	0.84 (0.61-1.15)
>200 grams of fruit per day	152	0.89 (0.68-1.16)	58	0.77 (0.48-1.24)	89	1.03 (0.73-1.45)	107	0.98 (0.72-1.35)
p for trend		>0.05		>0.05		>0.05		>0.05
Per 100 grams a day	480	0.94 (0.82-1.08)	134	0.88 (0.69-1.12)	241	1.02 (0.85-1.21)	310	1.00 (0.85-1.17)
Total fruit intake in current smokers								
<100 grams of fruit per day	183	1.00 (ref)	56	1.00 (ref)	106	1.00 (ref)	113	1.00 (ref)
100–200 grams of fruit per day	119	0.92 (0.72-1.17)	43	1.01 (0.67-1.52)	74	0.88 (0.65-1.19)	90	1.00 (0.75-1.33)
>200 grams of fruit per day	105	0.81 (0.61-1.07)	43	0.86 (0.54-1.36)	62	0.82 (0.58-1.17)	67	0.96 (0.69-1.33)
p for trend		>0.05		>0.05		>0.05		>0.05
Per 100 grams a day	407	0.90 (0.79-1.03)	142	0.93 (0.74-1.17)	242	0.90 (0.76-1.07)	270	0.98 (0.84-1.15)

[a] Model stratified by cohort, age at study entry, and sex (where applicable), and adjusted for smoking status and pack-years of cigarette smoking (where applicable), ethnicity, total vegetable consumption, alcohol intake, and total energy intake


Individuals in the BLEND study (n=726,355)
19 studies excluded for case-control design (n=29,898)
Individuals eligible for the pooled analysis (n=696,457)
3 cohort studies excluded for incomplete data on follow-up (n=99,226)
Individuals eligible for the pooled analysis (n=597,231)
Individuals excluded for missing data on
fruit intake (n=28,929)
smoking related variables (n=27,476)
ethnicity (n=472)
vegetable intake (n=173)
or for extreme values on total energy intake
(<800 kcal or >6000 kcal) (n=4277)
Individuals eligible for the pooled analysis (n=535,904)
Individuals excluded for incident bladder cancers diagnosed within the first two years of follow-up (n=191)
Individuals in the pooled analysis (n=535,713)