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Fruit consumption and the risk of bladder cancer

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1 Fruit consumption and the risk of bladder cancer: a pooled analysis

2 by the BLadder cancer Epidemiology and Nutritional Determinants

3 study

- 5 Sylvia H.J. Jochems^{1,2}, Raoul C. Reulen³, Frits H.M. van Osch^{1,2}, Willem J.A.
- 6 Witlox^{1,4}, Maria E. Goossens⁵, Maree Brinkman^{1,6,7}, Graham G. Giles^{7,8,9}, Roger L.
- 7 Milne^{7,8,9}, Piet A. van den Brandt¹⁰, Emily White¹¹, Elisabete Weiderpass¹², Inge
- 8 Huybrechts¹², Bertrand Hémon¹², Antonio Agudo¹³, Bas Bueno-de-Mesquita^{14,15,16,17},
- 9 K.K. Cheng³, Frederik J. van Schooten¹⁸, Richard T. Bryan², Anke Wesselius¹,
- 10 Maurice P. Zeegers^{1,2,19}
- 11
- 121.Department of Complex Genetics and Epidemiology, School of Nutrition and13Translational Research in Metabolism, Maastricht University, Maastricht, the14Netherlands
- Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham,
 United Kingdom
- Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom
- 194.Maastricht University Medical Centre+, Department of Clinical Epidemiology and20Medical Technology Assessment, Maastricht, The Netherlands
- 5. Cancer Centre of Sciensano, OD Public Health and Surveillance, Belgium
- Department of Clinical Studies and Nutritional Epidemiology, Nutrition Biomed
 Research Institute, Melbourne, Australia
- 24 7. Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, VIC, Australia
- 25 8. Centre for Epidemiology and Biostatistics, School of Population and Global Health,
 26 The University of Melbourne, Melbourne, VIC, Australia
- Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria Australia
- Department of Epidemiology, Schools for Oncology and Developmental Biology and
 Public Health and Primary Care, Maastricht University Medical Centre, Maastricht, the
 Netherlands
- 32 11. Fred Hutchinson Cancer Research Center, Seattle, Washington, United States
- International Agency for Research on Cancer (IARC), World Health Organization,
 Lyon, France
- 35 13. Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Institut Català
 36 d'Oncologia, L'Hospitalet de Llobregat, Spain
- Former senior scientist, Dept. for Determinants of Chronic Diseases (DCD), National
 Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
- Former associate professor, Department of Gastroenterology and Hepatology,
 University Medical Centre, Utrecht, The Netherlands
- 41 16. Former visiting professor, Dept. of Epidemiology and Biostatistics, The School of
 42 Public Health, Imperial College London, St Mary's Campus, Norfolk Place, London,
 43 United Kingdom
- 44 17. Former Academic Icon / visiting professor, Dept. of Social & Preventive Medicine,
 45 Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
- 46 18. Department of Pharmacology and Toxicology, NUTRIM School for Nutrition and
 47 Translational Research in Metabolism, Maastricht University, Maastricht, the
 48 Netherlands
- 49 19. CAPHRI School for Public Health and Primary Care, University of Maastricht, 50Maastricht, The Netherlands
- 51

5	2
5	4

53 Abbreviations

- 54 95% confidence interval = 95% CI
- 55 BLadder Cancer Epidemiology and Nutritional Determinants study = BLEND
- 56 Carcinoma In Situ = CIS
- 57 European Prospective Investigation into Cancer and Nutrition study = EPIC
- 58 Food Frequency Questionnaire = FFQ
- 59 Hazard Ratio = HR
- 60 Melbourne Collaborative Cohort Study = MCCS
- 61 Muscle invasive bladder cancer = MIBC
- 62 Netherlands Cohort Study = NLCS
- 63 Non-muscle invasive bladder cancer = NMIBC
- 64 VITamins And Lifestyle cohort study = VITAL
- 65 World Cancer Research Fund = WCRF
- 66
- 67

68 Novelty and impact statement

- 69 Previous studies often lacked adequate numbers with bladder cancer to detect
- 70 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
- 73 the risk of bladder cancer in women.

75 Abstract

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

- 78 associations between types of fruit and bladder cancer risk satisfactorily.
- 79 Fruit consumption in relation to bladder cancer risk was investigated by pooling
- 80 individual data from 13 cohort studies. Cox regression models with attained age as
- 81 time scale were used to estimate hazard ratios (HRs) for intakes of total fruit and
- 82 each of citrus fruits, soft fruits, stone fruits, tropical fruits, pome fruits, and fruit
- 83 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
- 86 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).
- 88 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-
- 90 0.92), the test for heterogeneity by bladder cancer subtype was non-significant (p-
- 91 heterogeneity=0.14). Increasing fruit consumption (by 100 gram/day) was not
- 92 associated with bladder cancer risk in men (HR=0.99; 95% CI 0.94-1.03), never
- 93 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
- 95 type of fruit was not found to be associated with bladder cancer risk (p-values>0.05).
- 96 This study supports no evidence that the consumption of specific types of fruit
- 97 reduces the risk of bladder cancer. However, increasing fruit consumption may
- 98 reduce bladder cancer risk in women.
- 99

100 Introduction

101 Bladder cancer is the ninth most common cancer worldwide, with almost 550,000 102 newly diagnosed cases in 2018 (1). Although cigarette smoking is the primary risk 103 factor for bladder cancer, the sex-based difference in bladder cancer incidence is 104 independent of differences in smoking status (2). Dietary factors may contribute to 105 bladder cancer risk considering that many dietary compounds are excreted in urine 106 (3). Fruits contain high levels of phytochemicals, minerals, and antioxidant nutrients, 107 that may hold anti-carcinogenic properties (4). According to a panel of experts of the 108 World Cancer Research Fund (WCRF) Continuous Update Project report 'Diet, 109 nutrition, physical activity and bladder cancer', there is limited evidence from cohort 110 studies that greater consumption of fruits and vegetables may decrease bladder 111 cancer risk (4). Moreover, adherence to the Mediterranean diet, rich in fruits, may 112 decrease the risk of bladder cancer (5). Results from case-control studies have 113 mainly shown inverse associations with fruit consumption, especially for the intake of 114 citrus fruits (6-8). However, recall bias and selection bias may have influenced the 115 reporting of fruit intake in case-control studies and most studies often lacked an 116 adequate number of individuals to detect associations between fruit intake and 117 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 118 cases can be substantially increased with the advantage that the association 119 120 between fruit intake and bladder cancer risk can be investigated with greater power 121 for different types of fruits and by sex, smoking status, and bladder cancer subtype. 122 In addition, fruit intake categories and covariates can be standardized across studies 123 (unlike in systematic reviews or meta-analyses). The aim of this large-scale study 124 was to build on previous results of the European Prospective Investigation into 125 Cancer and Nutrition (EPIC) studies (9,10) and investigates the association between 126 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 127 128 Determinants (BLEND) study.

129

130 Methods

131 Study population

132 The BLEND study is an international consortium that pools individual participant data

133 from international cohort studies and case-control studies. Details of the

134 methodology of the BLEND study have been described elsewhere (11). Briefly, a 135 total of 13 cohort studies had sufficient data to be eligible for inclusion in this study 136 (i.e. method of dietary assessment, geographical region, disease status). About 75% 137 of the study populations originated from centers in Europe including the EPIC studies 138 (12.13) and the Netherlands Cohort Study (NLCS) (14). Other populations originated from Australia (Melbourne Collaborative Cohort Study (MCCS)) (15) and North 139 140 America (VITamins And Lifestyle cohort study (VITAL)) (16). All studies have been 141 ethically approved and all study participants provided informed consent. 142 143 Bladder cancer ascertainment 144 Each study ascertained incident bladder cancers with International Classification of 145 Diseases (ICD-O-three code C67) using population-based cancer registries, health 146 insurance records, cancer registries, or medical records. Linkages to mortality registries were conducted during the follow-up period of each study. The term 147 148 bladder cancer is used for all urinary bladder neoplasms. Bladder cancers were 149 classified into non-muscle invasive bladder cancer (NMIBC) and muscle invasive 150 bladder cancer (MIBC). NMIBCs included noninvasive carcinomas confined to the 151 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 152 153 (carcinoma in situ; CIS). MIBCs included carcinomas that invaded into the detrusor 154 muscle (stage T2), carcinomas that invaded into the peri vesical tissue (stage T3), 155 and carcinomas that invaded adjacent tissues and organs (most often the prostate or 156 uterus) (stage T4). With bladder cancer representing a heterogeneous group of 157 tumours, that possibly develop through different but interrelated pathways (17) and 158 could have implications for treatments and outcomes, NMIBCs were further divided 159 into "lower" risk (stage Ta with a low grade (grade 1 or grade 2)) and "higher" risk 160 (stage Ta with grade 3, stage T1, and CIS). Whilst lower-risk NMIBC often occurs 161 from papillary tumours, higher-risk NMIBC and MIBC are more likely to develop from

162 163

164 Dietary assessment

non-papillary tumours (18).

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 168 data collected from the study specific FFQs and to consider the varying portions 169 sizes between different populations, frequency intakes were converted to grams 170 using the portion sizes described in the FFQ of each study. Where applicable, fruit 171 intakes were converted from weekly, monthly, or yearly intakes, to daily intakes. The 172 consumption of fruits in grams per day was then standardised across studies by 173 making use of the Eurocode 2 food coding system (19). Total fruit intake was 174 computed as the sum of grams of all fruit items or fruit groups (excluding fruit juices) 175 provided by each study. The following types of fruits were defined: citrus fruits, pome 176 fruits, soft fruits, stone fruits, tropical fruits, and fruit products (Table 1).

177

178 Statistical analysis

179 Person-years of follow-up for each participant were calculated from date of study 180 enrolment until the date of a first bladder cancer diagnosis, death, emigration, last 181 known contact, or end of study follow-up, whichever came first. For the NLCS, a 182 nested case-cohort approach was applied, in which the number of person-years at 183 risk was estimated based on a subcohort that was randomly sampled after baseline 184 (14). Total fruit consumption was analysed both as a continuous variable (expressing 185 results per 100 grams per day in usual total fruit consumption), and a categorical 186 variable. For the categorical variable, total fruit consumption was divided into four 187 intake categories: <100 grams of fruit per day (less than approximately one piece of 188 fruit), 100-200 grams of fruit per day (approximately one to two pieces of fruit), 200-189 300 grams of fruit per day (approximately two to three pieces of fruit), and >300 190 grams of fruit per day (more than approximately three pieces of fruit), using the 191 lowest intake category as a reference. Fruit types (citrus fruits, soft fruits, stone fruits, 192 tropical fruits, pome fruits, and fruit products) were each analysed as a continuous 193 variable per 25 grams of fruits per day increase and were modelled into guartiles. 194 using the lowest quartile as a reference. Cox proportional hazard models with 195 attained age as time scale were used to calculate hazard ratios (HR) and 95% 196 confidence intervals (95% CI) for bladder cancer. The assumption of proportional 197 hazards was examined for the relationship of scaled Schoenfeld residuals with time 198 and appeared to be violated when considering all participants together (20). Based 199 on a priori reasons and the violation of the proportional hazard assumption for all 200 participants, analyses were performed for sex, smoking status (never smokers, 201 former smokers, current smokers), and bladder cancer subtype (NMIBC and MIBC,

202 and further classification into lower-risk NMIBC and higher-risk NMIBC); the 203 assumption of proportional hazards was now found to be satisfied in all models. 204 Heterogeneity was calculated by the duplication method for Cox regression as 205 described by Lunn et al. (21), using a likelihood ratio test to compare the model with 206 and without interaction terms between total fruit consumption and sex, smoking 207 status, and bladder cancer subtype. Within the regression models, all analyses were 208 stratified by cohort, sex, and age at study enrolment. Adjustment was made for the 209 potential confounders smoking status (current smoker/former smoker/never smoker), 210 pack-years of cigarette smoking (continuous in years), ethnicity 211 (Asian/Black/Caucasian), total vegetable consumption (continuous in gram/day), 212 alcohol intake (continuous in gram/day), and total energy intake (continuous in 213 kcal/day). A sensitivity analysis was performed on pre-defined sex-specific energy 214 intake cut offs (800-4000 kcal/day for women and 1500-6000 kcal/day for men). All 215 statistical analyses were performed using Stata software version 14 and a two-sided 216 p-value of <0.05 was considered statistically significant. 217

218 Data Availability

219 The data that support the findings of this study are not publicly available, but data will

220 be made available upon reasonable request.

221

222

223 Results

224 Baseline characteristics of the study samples included are presented in Table 2. Of

225 597,231 potentially eligible participants, 61,327 individuals were excluded from the

226 statistical analyses for having missing data on total fruit consumption (n=28,929),

227 total vegetable consumption (n=173), ethnicity (n=472), pack-years of smoking

228 (n=27,476), or for missing and extreme values (<800 kcal/day and >6000 kcal/day)

229 of total energy intake (n=46,906). In addition, individuals with incident bladder

230 cancers diagnosed within the first two years of study follow-up were excluded

- 231 (n=191) (Figure 1). During an average of 11.2 years of follow-up, 2836 of the
- 232 remaining 535,713 participants were diagnosed with an incident bladder cancer. A
- 233 total of 1135 cases were classified as NMIBC and 706 as MIBC; 995 bladder
- 234 cancers could not be classified due to missing data on tumour characteristics.

236 Total fruit

237 In men, increasing fruit consumption by 100 grams per day was not associated with 238 overall bladder cancer risk (HR=0.99; 95% CI 0.94-1.03) (Table 3), or with any 239 bladder cancer subtype (p-heterogeneity=0.33) (Table 4). The sensitivity analysis on 240 sex-specific cut offs for total energy intake in men per 100 grams of fruit per day 241 increase showed a comparable result (HR=0.99; 95% CI 0.94-1.04). Compared with 242 the lowest category of fruit intake (<100 grams of fruit per day), the highest total fruit 243 intake category (>300 grams of fruit per day) was associated with a lower risk of 244 overall bladder cancer in women (HR=0.75; 95% CI 0.59-0.97) (Table 3). In the 245 continuous analysis for women, increasing total fruit consumption by 100 grams per 246 day was inversely associated with the risk of overall bladder cancer (HR=0.92; 95% 247 CI 0.85-0.99) (Table 3). A similar result for increasing total fruit consumption and 248 bladder cancer risk in women was obtained from the sensitivity analysis when sex-249 specific cut offs for total energy intake were used (HR=0.92; 95% 0.85-0.99). 250 Although in women the association was stronger for higher-risk NMIBC (HR=0.72; 251 95% CI 0.56-0.92) than for all NMIBCs combined (HR=0.79; 95% CI 0.67-0.94), the 252 test for heterogeneity by bladder cancer subtype did not reach significance (p-253 heterogeneity=0.14) (Table 4). In the subgroup analysis on smoking status, the 254 consumption of fruit was not associated with the risk of bladder cancer in never 255 smokers (HR=0.96; 95% CI 0.88-1.05), former smokers (HR=0.98; 95% CI 0.92-256 1.05), current smokers (HR=0.95; 95% CI 0.89-1.01) (Table 3), or ever smokers 257 (current and former smokers combined) (HR=0.96; 95% CI 0.92-1.01).

258

259 Subtypes of fruit

In women, no associations were found between increasing consumption by 25

- 261 grams per day of citrus fruits (HR=0.97; 95% CI 0.92-1.03), soft fruits (HR=0.95;
- 262 95% CI 0.84-1.09), stone fruits (HR=0.94; 95% CI 0.85-1.03), pome fruits (HR=0.95;
- 263 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
- 266 (highest quintile vs. lowest quintile HR=0.78; 95% CI 0.62-0.99, p-trend=0.05), the
- 267 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).

271

272 Discussion

273 In this analysis of pooled data from 13 prospective cohort studies, comprising 2836 274 individuals with incident bladder cancer, an association was found between 275 increasing total fruit consumption and a decreased risk of bladder cancer in women. 276 No associations were found between fruit consumption and the risk of bladder 277 cancer for men, current smokers, former smokers, or never smokers (9,10). With 278 bladder cancer being a heterogeneous disease, attention has increasingly focused 279 on investigating subtypes of bladder cancer. While in the EPIC study, tumours were 280 defined as non-aggressive urothelial cell carcinomas or aggressive urothelial cell 281 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 282 283 differences between the risk associations for the bladder cancer subtypes in relation 284 to the consumption of fruit using the duplication method for Cox regression as 285 described by Lunn et al. (21). The addition of incident bladder cancers from three 286 additional large cohorts (NLCS, MCCS, and VITAL) could explain the novel finding 287 for the inverse association between total fruit consumption and bladder cancer risk 288 for women. Although most prospective studies on bladder cancer risk found no 289 associations with fruit consumption (22–25), the findings for women are in partial 290 agreement with results of the Multiethnic Cohort study (26). Park et al. (26) found 291 that only for women, total fruit and citrus fruit consumptions were inversely 292 associated with the risk of bladder cancer (HR=0.54; 95% CI 0.34-0.85 and 293 HR=0.56; 95% CI 0.34-0.90, respectively). Interestingly, the authors showed that 294 there was only a significant association with fruit consumption for women when 295 considering invasive bladder cancer as an endpoint, not non-invasive bladder cancer 296 (26). Results from the Nurses' Health study on lung cancer (a smoking-related 297 cancer as bladder cancer) also showed that especially women with greater intakes of 298 fruit had a reduced risk of cancer (27). It cannot be excluded that the inverse 299 association found for women but not men may be partially explained by differences 300 in hormonal factors (e.g. estrogen) and urination habits between men and women, or 301 by residual confounding by smoking habits, though the inverse association for women in the Multiethnic Cohort study was found after rigorous adjustment for 302

303 cigarette smoking and reproductive factors (26). Although statistical power was more 304 limited for women compared with men (683 incident bladder cancers in women and 305 2153 incident bladder cancers in men), especially in the categorical analysis of fruit 306 intake, the number of incident bladder cancers in the continuous analyses for 307 increasing total fruit consumption by 100 grams per day in women had adequate 308 power. All types of fruit showed non-significant associations with the risk of bladder 309 cancer (all p>0.05) and therefore the inverse association between fruit consumption 310 and bladder cancer risk in women cannot be attributed to increased consumption of 311 a specific type of fruit.

312 This study has several strengths, including the large sample size providing statistical 313 power to examine different types of fruits, the possibility to classify risks by sex, 314 smoking status, and bladder cancer subtype, and the inclusion of studies from 12 315 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) 316 317 and the Multiethnic Cohort study (26) on fruit consumption and bladder cancer risk 318 indicated that after applying a calibration method (28), there were no substantial 319 differences between their observed findings and their calibrated estimates. Although 320 by making use of the Eurocode 2 Food Coding System (19) the potential for 321 misclassification for the types of fruit is limited, measurement error in the dietary 322 assessment by limitations of the FFQs, including over- and under-reporting of usual 323 fruit consumption, and the inability to investigate dietary changes over time with only 324 one single measurement of fruit at time of study entry, cannot be excluded. However, 325 if changes in dietary intake were made by individuals during follow-up, it would still 326 be questionable whether these changes would have influenced bladder cancer risk 327 in this relatively short period of time. Other limitations of this study were the limited 328 information on covariates that may be associated with the risk of bladder cancer (and 329 that are highly correlated with fruit consumption), such as body mass index, physical 330 activity, and socioeconomic status. However, it has been indicated that these factors 331 may probably account for only a small percentage of bladder cancer cases overall 332 (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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340	
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342	On behalf of all authors, the corresponding author states that there is no conflict of
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344	
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347	on Cancer / World Health Organization, the authors alone are responsible for the
348	views expressed in this article and they do not necessarily represent the decisions,
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481		

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	EPIC	EPIC	EPIC	EPIC	EPIC	EPIC	EPIC	EPIC	EPIC	NLCS	MCCS	VITAL	Total in
	Denmark	France	Germany	Greece	Italy	The Netherlands	Norway	Spain	Sweden	United Kingdom	The Netherlands	Australia	USA	BLEND
											(case-cohort design)			study
	No.a (%) /	No.ª (%) /	No.ª (%) /	No.ª (%) /	No.a (%) /	No.a (%) /	No.ª (%) /	No.ª (%) /	No.ª (%) /	No.ª (%) /	No.a (%) /	No.ª (%) /	No.ª (%) /	No.ª (%) /
	(mean (SD))	(mean (SD))	(mean (SD))	(mean (SD))	(mean (SD))	(mean (SD))	(mean (SD))	(mean (SD))	(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

·····	Full cohort		p	Males		Females		Never smokers		Former smokers		Current smokers	
	Cases	HR ^{a,b} (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)	

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

^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		rrent smokers
	Cases	HR ^{a,b} (95% CI)	Cases	HR ^a (95% CI)	Cases	HR ^a (95% CI)	Cases	HR ^a (95% CI)	Cases	HRª (95% CI)	Cases	HRª (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			her-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

