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ORIGINAL PAPER

Prospective study of the association between grapefruit intake and risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC)

Elizabeth A. Spencer · Timothy J. Key · Paul N. Appleby · Carla H. van Gils · Anja Olsen · Anne Tjønneland · Françoise Clavel-Chapelon · Marie-Christine Boutron-Ruault · Marina Touillaud · Maria-José Sánchez · Sheila Bingham · Kay Tee Khaw · Nadia Slimani · Rudolf Kaaks · Elio Riboli

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Abstract Grapefruit inhibits cytochrome P450 3A4 and may affect estrogen metabolism. In the European Prospective Investigation into Cancer and Nutrition (EPIC), we examined the relationships of grapefruit intake with risk of breast cancer and with serum sex hormone levels. 114,504 women with information on dietary intake of grapefruit and on reproductive and lifestyle risk factors were followed for a median 9.5 years and 3,747 incident breast cancers were identified. Fifty-nine percent of women reported eating grapefruit, 4% ate $\geq$ 60 g/day. Cox proportional hazard models were used to estimate the hazard ratio (HR) for breast cancer according to grapefruit intake, adjusting for study centre, reproductive factors, body mass index, energy intake, and alcohol intake. Grapefruit intake was not related to the risk of breast cancer: compared with women who ate no grapefruit, women with the highest intake of $\geq$60 g/day had a HR of 0.93 (95% CI 0.77–1.13), p for linear trend = 0.5. There was no relationship between grapefruit intake and breast cancer risk among premenopausal women, all postmenopausal women, or postmenopausal women categorized by hormone replacement therapy use (all p>0.05). There was no association between grapefruit intake and estradiol or

E. A. Spencer (✉) · T. J. Key · P. N. Appleby
Cancer Epidemiology Unit, University of Oxford, Oxford, UK
e-mail: elizabeth.spencer@ceu.ox.ac.uk

C. H. van Gils
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

A. Olsen · A. Tjønneland
Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark

F. Clavel-Chapelon · M.-C. Boutron-Ruault · M. Touillaud
INSERM (Institut National de la Santé et de la Recherche Médicale), ERI 20, EA 4045, and Institut Gustave Roussy, Villejuif Cedex 94805, France

M.-J. Sánchez
Andalusian School of Public Health, Granada, Spain

M.-J. Sánchez
CIBER Epidemiología y Salud Pública (CIBERESP), Granada, Spain

S. Bingham
Department of Public Health and Primary Care, MRC Dunn Human Nutrition Unit, University of Cambridge, Cambridge, UK

S. Bingham
Department of Public Health and Primary Care, MRC Centre for Nutritional Epidemiology in Cancer Prevention and Survival, University of Cambridge, Cambridge, UK

K. T. Khaw
Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

N. Slimani
International Agency for Research on Cancer, The World Health Organisation, Lyon, France

R. Kaaks
Division of Cancer Epidemiology, German Cancer Research Centre, Heidelberg, Germany

E. Riboli
Department of Epidemiology and Public Health, Imperial College, London, UK

estrone among postmenopausal women. In this study, we found no evidence of an association between grapefruit intake and risk of breast cancer.

Keywords Breast cancer · CYP3A4 metabolism · Grapefruit intake · Prospective studies

Introduction

Grapefruit inhibits the intestinal cytochrome P450 3A4 (CYP3A4) system [1, 2] and interferes with the metabolism of orally administered hormone preparations and drugs [3–5]. A recent publication from the Multiethnic Cohort showed a positive association between intake of grapefruit and risk of breast cancer among postmenopausal women [6], and a separate publication from that cohort reported a positive association between high intakes of grapefruit and serum endogenous estrogen concentrations among postmenopausal women, suggesting that this was probably due to the inhibition of the CYP3A4 enzyme system [7]. However, a subsequent report from the Nurses' Health Study showed no association between consumption of grapefruit and risk of breast cancer and no association between grapefruit intake and serum sex hormone concentrations [8]. We examined the association between intake of grapefruit and risk of breast cancer among 114,504 women in the European Prospective Investigation into Cancer and Nutrition (EPIC), and among subgroups of women categorized by menopausal status and hormone replacement therapy (HRT) use. We also examined the cross-sectional association between consumption of grapefruit and serum concentrations of sex hormones among a subset of 940 women for whom serum hormone concentrations had been measured.

Materials and methods

The EPIC is a multi-center prospective cohort study including participants recruited at 23 coordinating centers in 10 European countries: Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, and the United Kingdom (UK). The design and methods for this study have been described in detail previously [9].

Participants

Briefly, participants were mainly recruited from the general population residing in a particular geographical region. Eligible individuals were invited to participate in EPIC and those who accepted gave informed consent and completed questionnaires on their diet, lifestyle, and medical history. Most study participants had anthropometric measurements including height and weight taken at a study center.

In this study, we examined the relationship between the dietary intake of grapefruit and risk of breast cancer; therefore, we describe data for the female participants of the EPIC cohort for whom data on grapefruit intake were available. Dietary intakes were measured using country-specific questionnaires, designed to capture local dietary habits [9]. For some centers, information on intake of grapefruit or grapefruit juice was assessed in combination with intake of orange or other citrus fruits. These data were not used in this study. Centers for which information on grapefruit as an individual item was available for the majority of participants were those in Denmark (two centers), France (six centers), and the UK (three centers, with the Oxford center divided into two, one for the general population and one for the health conscious participants). Data on intake of grapefruit juice were available for only a small number of women and so were not included in these analyses.

Data for women with prevalent cancer at the time of recruitment or with missing or incomplete dietary or non-dietary questionnaires were excluded, as were data for individuals in the top and bottom 1% of the ratio of energy intake to estimated energy requirement (calculated from age, sex, and body weight) to reduce the effect of implausible extreme values (16,603 women). This left data for 149,431 participants from three countries. A number of these women had missing data for one or more breast cancer risk factors (number of full-term pregnancies, age at first birth, menopausal status, age at menopauses, use of HRT, age at menarche, body mass index (BMI), energy intake, or alcohol intake). For the main analyses, women with missing data for one or more of these covariables were excluded for the analyses, which left 114,504 women in the analysis. The analyses were then repeated among the full 149,431 women, assigning women with missing values to a separate category for that variable, and these additional results are reported in the text.

Sex hormone data

Concentrations of the sex hormones androstenedione, dehydroepiandrosterone sulfate (DHEAS), testosterone, estrone and estradiol, and sex hormone binding globulin (SHBG) were measured in the sera of 940 women for whom we also had information on grapefruit intake. The biological samples were taken at recruitment to the study, and the measurement of sex hormones was as described previously [10–13]. Participants were controls in previously published nested case–control analyses of various biomarkers and breast, ovarian or endometrial cancer risk, and detailed descriptions of these nested case–control studies have been published elsewhere [10–13].

Not all 940 women had data for all of the hormones measured: androstenedione was measured in 927 women; DHEAS in 876 women; testosterone in 835 women; estrone in 117 premenopausal and 408 postmenopausal women; and estradiol in 88 premenopausal women and 431 postmenopausal women. Due to the low numbers of premenopausal women for whom estrone and estradiol concentrations were known, results for these hormones are presented only for postmenopausal women.

End point data

Follow-up was via population cancer registries in Denmark and the UK, and in France used a combination of methods including health insurance, cancer and pathology registries, and biennial active follow-up, with case information confirmed by medical records [9, 14]. Mortality data were obtained from either the cancer or the mortality registries at the regional or national level. Cancers were coded using the International Classification of Diseases for Oncology, Second Edition (ICD-O-2) and breast cancer was defined as C50.0–50.9. The women were followed from enrollment into the study (1993–2000) until the first breast cancer diagnosis, death, emigration, or end of the follow-up period (1993–2006).

Statistical methods

Hazard ratios (HRs) and their 95% CI were estimated using Cox regression models with age as the underlying time variable. The analyses were stratified by center (to control for effects related to different follow-up procedures and questionnaire design), number of full-term pregnancies (0, 1, 2, 3, 4, or more, unknown), age at first birth (nulliparous, <20, 20–24, 25–29, 30 years and over, unknown), age at menopause/menopausal status [not postmenopausal (i.e., pre or perimenopausal), <45, 45–49, 50–54, 55 years and over, unknown], use of menopausal hormones (HRT) (never, former, current, unknown), and adjusted for age at menarche (<13, 13, 14, 15+ years, never menstruated, unknown), BMI (weight in kg/height in m^2) (<20, 20 to <25, 25 to <30, 30+ kg/m^2), energy intake (kJ/day, continuous), and alcohol intake (<1, 1–7, 8–15, 16+ g/day ethanol).

Grapefruit intake was divided into five categories (none, 1 to <10, 10 to <30, 30 to <60, ≥60 g/day) with the lowest intake category as the reference group. Simple tests of linear trend in the risks were performed by replacing the categorical grapefruit intake variable with the continuous intake variable in the Cox regression models. Analyses were performed for all countries combined and also separately for each of Denmark, France, and the UK. Analyses were performed among all women, and because risk factors for breast cancer may vary by menopausal status, also separately for postmenopausal women and premenopausal women. Due to potential biological interactions between hormone replacement therapy and grapefruit consumption, we repeated the analyses among postmenopausal women categorized by the use of hormone replacement therapy. Statistical significance was set at the 5% level.

The cross-sectional association between grapefruit consumption and concentrations of sex hormones was evaluated by calculating geometric mean concentrations of each hormone within each category of grapefruit intake. A test for trend of the association between grapefruit consumption and each hormone concentration was performed using grapefruit intake as a continuous variable.

We combined the results from this study with the two previously published studies on grapefruit intake and risk of breast cancer [6, 8]. Results for postmenopausal women only were available from all three studies. In each study, the lowest category of intake was zero. The highest category of intake for this study and for the study by Monroe et al. was ≥60 g/day [6]. The highest category of intake for the study by Kim and co-workers was reported to be ≥1/4 grapefruit/day; if a whole grapefruit is estimated to be 240 g (as reported in [6]) this corresponds to ≥60 g/day. The comparison in each case is therefore between women with ≥60 g intake per day and women with zero consumption. We estimated the summary HR for the pooled data from the individual studies, calculated as the weighted average of the individual HR, with the weighting proportional to the inverse of the variance of each HR.

Results

Grapefruit consumption and breast cancer risk

Over a median 9.5 years of follow-up, 3,747 cases of breast cancer among 114,504 women were recorded. Fifty-nine percent of these women reported eating some grapefruit, 13% of women consumed 30 g/day or more, and 4% of women ate 60 g/day or more (Table 1). Higher grapefruit consumption was associated with older age: among women eating no grapefruit, mean age was 49 years and among women consuming 60 g/day or more of grapefruit, mean age was 53 years. Energy intake was higher among women consuming more grapefruit: among women with zero intake of grapefruit, mean energy intake was 1,970 kcal/day and among women consuming 60 g/day or more of grapefruit, mean energy intake was 2,148 kcal/day. Grapefruit consumption was also associated with number of full-term pregnancies, age at first birth, age at menopause, BMI, and alcohol intake but these associations were not linear (data not shown). These factors were adjusted for in analyses of grapefruit intake and risk of breast cancer.

Table 1 Number of breast cancer cases and intake of grapefruit by country

Country	Women at risk	Cases	Percentage of women within each category of grapefruit consumption (g/day)				
			None	1 to <10	10 to <30	30 to <60	≥60
Denmark	22,989	648	28	58	7	5	4
France	48,677	2,282	33	14	35	14	3
UK	42,838	817	57	24	10	6	4
Total	114,504	3,747	41	27	20	9	4

Table 2 Breast cancer risk factors among cases and non-cases

Risk factor	Cases (n = 3,747)	Non-cases (n = 110,757)	All women (n = 114,504)
Age at recruitment, mean (SD), years	52.6 (7.2)	49.8 (10.5)	49.9 (10.4)
Age at menarche, mean (SD), years	13.0 (1.5)	13.0 (1.5)	13.0 (1.5)
Number of full-term pregnancies, mean (SD)	1.9 (1.1)	1.8 (1.2)	1.8 (1.2)
Age at first birth (parous women only, mean (SD))	25.4 (4.5)	25.0 (4.3)	25.0 (4.3)
Menopausal status (%)			
Premenopausal	27.2	37.7	37.3
Perimenopausal	27.4	21.2	21.4
Postmenopausal	41.9	38.2	38.3
Bilateral ovariectomy	3.5	2.9	3
Age at menopause (postmenopausal women only, mean (SD))	49.6 (5.0)	49.1 (5.1)	49.1 (5.1)
Use of HRT (postmenopausal women only) (%)			
Never	49.2	60.2	59.8
Former	18.5	18.0	18.1
Current	32.4	21.8	22.2
Body mass index, mean (SD), kg m^{-2}	24.0 (4.0)	24.0 (4.1)	24.0 (4.1)
Alcohol consumption, mean (SD), g/day ethanol	11.4 (14.1)	10.2 (13.1)	10.3 (13.1)

Table 2 shows breast cancer risk factors among cases and non-cases. Mean age was higher in the cases than in the controls, at 52.6 versus 49.8 years. A slightly higher proportion of cases were postmenopausal at recruitment compared with the non-cases (42 vs. 38%). A higher proportion of the cases than non-cases were currently using hormone replacement therapy (32 vs. 22%) and a higher proportion of non-cases were never-users of HRT (60 vs. 49%).

There was no evidence of an association between grapefruit consumption and risk of breast cancer (Table 3). Compared with women who ate no grapefruit, HRs across increasing categories of grapefruit consumption were 1 to <10 g/day, 0.94 (95% CI 0.86–1.04); 10 to <30 g/day, 1.02 (0.94–1.12); 30 to <60 g/day, 0.99 (0.88–1.11); ≥60 g/day, 0.93 (0.77–1.13); $p = 0.5$ for trend. There were no significant associations between grapefruit intake and breast cancer risk for women recruited in Denmark ($p = 0.7$ for trend), France ($p = 0.7$), or the UK ($p = 0.4$) (detailed data not shown). When the analysis was performed using only adjustment for age (not adjusting for the other covariables), the results did not differ; thus only results from the multivariable analyses are presented here.

Among postmenopausal women, compared with women who did not eat grapefruit, HRs in increasing categories of grapefruit consumption were as follows: 1 to <10 g/day, 0.92 (95% CI 0.80–1.07); 10 to <30 g/day, 1.16 (1.00–1.35); 30 to <60 g/day, 0.95 (0.78–1.14); ≥60 g/day, 0.97 (0.75–1.27); $p = 0.6$ for trend. There were no associations between grapefruit intake and breast cancer risk for postmenopausal women who never used HRT (p for trend = 0.8), postmenopausal women who formerly used HRT (p for trend = 0.4), postmenopausal women using HRT at recruitment (p for trend = 0.7), or premenopausal women (p for trend = 0.2).

When we repeated these analyses among the dataset of 149,431 women, including 34,907 women who had missing data for one or more of the covariables (number of full-term pregnancies, age at first birth, menopausal status/age at menopause, use of HRT, age at menarche, BMI, energy intake, and alcohol intake), assigning women with a missing value to a separate category for that variable, the results were very similar. During follow-up of these women, 5,203 incident cases of breast cancer were identified. For all women, there was no evidence of an association between grapefruit intake and breast cancer risk: the HRs for categories of intake 1 to <10, 10 to <30, 30 to <60, ≥60 g/day were 0.99 (0.91–1.07), 1.02 (0.95–1.10), 1.01 (0.91–1.11), 1.03 (0.88–1.20), respectively, p for trend 0.9. There was no evidence of association within any of the groups of women categorized by menopausal status and HRT use (p for trend 0.3–0.9).

Table 3 Association between grapefruit intake and risk of breast cancer in EPIC

	Grapefruit intake g/day					Test for trend[b]
	0	1 to <10	10 to <30	30 to <60	≥60	
All women						
No. of cases	1,346	875	986	410	130	
HR (95% CI)[a]	1.00 (ref)	0.94 (0.86–1.04)	1.02 (0.94–1.12)	0.99 (0.88–1.11)	0.93 (0.77–1.13)	0.5
All postmenopausal women						
No. of cases	528	397	399	173	73	
HR (95% CI)[a]	1.00 (ref)	0.92 (0.80–1.07)	1.16 (1.00–1.35)	0.95 (0.78–1.14)	0.97 (0.75–1.27)	0.6
Postmenopausal HRT never-users						
No. of cases	260	191	203	75	43	
HR (95% CI)[a]	1.00 (ref)	0.95 (0.77–1.17)	1.25 (1.02–1.53)	0.87 (0.66–1.14)	1.20 (0.85–1.68)	0.8
Postmenopausal HRT former users						
No. of cases	103	70	71	36	10	
HR (95% CI)[a]	1.00 (ref)	0.79 (0.56–1.12)	1.01 (0.71–1.43)	0.91 (0.59–1.39)	0.63 (0.31–1.29)	0.4
Postmenopausal HRT current users						
No. of cases	165	136	125	62	20	
HR (95% CI)[a]	1.00 (ref)	0.96 (0.74–1.24)	1.12 (0.86–1.47)	1.12 (0.81–1.55)	0.81 (0.48–1.37)	0.7
Premenopausal women						
No. of cases	374	215	289	112	28	
HR (95% CI)[a]	1.00 (ref)	1.01 (0.85–1.20)	1.05 (0.89–1.24)	1.15 (0.92–1.43)	1.19 (0.81–1.75)	0.2

[a] Age as the underlying time variable, stratified by center, number of full-term pregnancies, age at first birth, menopausal status/age at menopause, and use of hormones, and adjusted for age at menarche, BMI, energy intake, and alcohol intake

[b] p value from a test for trend using grapefruit intake as a continuous variable

Grapefruit intake and sex hormones

The cross-sectional association between grapefruit consumption and sex hormones is shown in Table 4. There was a positive association between grapefruit intake and SHBG: the mean SHBG among women consuming 0, 1 to <10, 10 to <30, 30 to <60, ≥60 g/day of grapefruit were 41.4 (95% CI 39.2–43.6), 37.7 (35.6–40.0), 41.6 (37.8–45.9), 44.1 (39.2–49.6), and 48.1 (41.1–56.3) (p for linear trend = 0.03). There was no evidence of an association between grapefruit intake and any other hormone (p for linear trend 0.2–0.9).

Meta-analysis of data on postmenopausal women in three studies

We combined the results from this study with the two previously published studies on grapefruit intake and risk of breast cancer [6, 8]. Data were available for postmenopausal women in all three studies, including 1,657 cases in the Multiethnic Cohort Study [6], 3,570 cases in the Nurses' Health Study [8] and 1,570 cases in the present study. For postmenopausal women consuming 60 or more gram grapefruit per day, the overall HR compared with women consuming no grapefruit was 1.06 (95% CI 0.95–1.19), based on 6,797 cases of breast cancer (Table 5).

Discussion

In this cohort of 114,504 women followed over 9.5 years, there was no evidence of an association between grapefruit intake and risk of breast cancer, either within groups of women categorized according to menopausal status and hormone replacement therapy use, or overall. There was no association between grapefruit consumption and serum levels of androstenedione, DHEAS, testosterone, estrone, or estradiol, although a positive relationship was observed between intake of grapefruit and serum SHBG.

These results do not support the findings of Monroe and colleagues, who reported a positive association between grapefruit consumption and risk of breast cancer among postmenopausal women in the Multiethnic Cohort Study [6], but are in line with the findings reported for women in the Nurses' Health Study by Kim et al. [8] showing no association overall. In the latter study, there was some evidence of an inverse relationship between grapefruit intake and risk of breast cancer among women who never used hormone replacement therapy. In contrast, we found no association between grapefruit intake and breast cancer risk among postmenopausal women who had never used hormone replacement therapy.

Grapefruit inhibits the intestinal cytochrome P450 3A4 (CYP3A4) system [1, 2] and interferes with the metabolism

Table 4 Geometric mean (95% CI) serum sex hormone concentrations among women with different intakes of grapefruit

	Grapefruit intake g/day					*p* for trend[b]
	0	1 to <10	10 to <30	30 to <60	≥60	
Pre- and postmenopausal women						
Androstenedione (nmol/l)[a]	3.63 (3.45–3.81)	3.69 (3.49–3.90)	3.66 (3.35–4.00)	3.76 (3.38–4.20)	3.64 (3.13–4.24)	0.9
No. of women = 927	389	303	119	77	39	
DHEAS (nmol/l)[a]	2,317 (2,166–2,479)	2,233 (2,072–2,407)	2,304 (2,039–2,603)	2,223 (1,917–2,577)	2,147 (1,756–2,625)	0.5
No. of women = 876	359	293	110	74	40	
Testosterone (nmol/l)[a]	1.24 (1.18–1.30)	1.29 (1.22–1.37)	1.38 (1.25–1.51)	1.22 (1.08–1.37)	1.11 (0.95–1.30)	0.2
No. of women = 835	348	275	104	69	39	
SHBG (nmol/l)[a]	41.4 (39.2–43.6)	37.7 (35.6–40.0)	41.6 (37.8–45.9)	44.1 (39.2–49.6)	48.1 (41.1–56.3)	0.03
No. of women = 876	360	295	108	73	40	
Postmenopausal women only						
Estrone (pmol/l)[a]	138 (129–149)	142 (130–154)	141 (124–160)	145 (124–169)	144 (121–171)	0.8
No. of women = 408	171	122	52	35	28	
Estradiol (pmol/l)[a]	90 (85–96)	84 (78–90)	92 (82–103)	89 (77–102)	90 (77–106)	0.7
No. of women = 431	177	129	58	38	29	

[a] Adjusted for batch, laboratory protocol, age at blood collection, smoking, BMI, alcohol, energy intake, and menopausal status/phase of the menstrual cycle where appropriate

[b] Test for trend obtained using grapefruit intake as a continuous variable

Table 5 Meta-analysis of the association between grapefruit intake and risk of breast cancer among postmenopausal women in three prospective studies

Study	Number of cases among postmenopausal women	HR (95% CI)[a]
Monroe et al. [7]	1,657	1.30 (1.06–1.58)
Kim et al. [8]	3,570	0.97 (0.83–1.14)
EPIC 2009	1,570	0.97 (0.75–1.27)
Overall	6,797	1.06 (0.95–1.19)

[a] Hazard ratio for ≥60 g/day intake of grapefruit compared with none

of orally administered hormone preparations and drugs [3–5]. The Multiethnic Cohort Study group published a report describing the relationship between dietary fiber intake and endogenous serum hormone concentrations among postmenopausal Mexican American women participating in the Multiethnic Cohort Study [7], including associations between grapefruit consumption and serum sex hormone concentrations. Among 242 women, those with high grapefruit consumption had higher concentrations of estrone, although there was no association for estradiol. The authors suggested that since grapefruit consumption was associated with endogenous estrone levels, it may also affect nonintestinal CYP3A4 levels. Thus, by inhibiting cytochrome P450 3A4, grapefruit may affect estrogen metabolism and therefore influence circulating levels of this hormone. Kim et al. subsequently reported no correlation between grapefruit or grapefruit juice consumption and plasma estradiol, estrone, or estrone sulfate in 701 postmenopausal Nurses' Health Study participants not using hormone replacement therapy [8]. In the present study, whilst we found some evidence of a positive association between grapefruit intake and SHBG, there was no evidence of an association between grapefruit intake and estradiol or estrone. Thus, our results do not support the hypothesis that high grapefruit intake increases levels of circulating estradiol or estrone. Further studies with data for a higher number of women would clarify this issue.

To our knowledge, a positive association between grapefruit intake and serum SHBG has not been previously reported. There may be a biological reason for this association, or this finding may represent confounding by a lifestyle factor not assessed in this study.

Since grapefruit consumption interferes with the metabolism of orally administered hormone preparations and drugs [3–5], women taking oral hormone therapy may be more susceptible to the influence of grapefruit on the cytochrome P450 system. We had insufficient data to assess the association between grapefruit consumption and serum sex hormones among postmenopausal women who were using hormone replacement therapy; however, we found no evidence of increased breast cancer risk associated with high grapefruit intake among postmenopausal women taking hormone replacement therapy.

In this study, we were not able to assess intakes of grapefruit juice, since on most food frequency questionnaires in

EPIC it was combined with orange juice intake. Kim et al. assessed intake of grapefruit juice in relation to risk of breast cancer in the Nurses' Health Study [8], but found no association. Grapefruit juice may be consumed more regularly and in greater amounts than whole grapefruit, so it may be worthwhile examining the association between breast cancer risk and grapefruit juice intake as well as whole grapefruit intake in future studies.

The distribution of grapefruit intake in this study appears to be broadly similar to those found in the Multiethnic Cohort Study and the Nurses' Health Study, although a lower proportion of women consumed 60 or more grams of grapefruit per day in this study than in the Multiethnic Cohort Study [6]. It is possible that due to this, the study was not able to detect a true association between high intakes of grapefruit and increased risk of breast cancer.

When we estimated a summary HR for breast cancer for women with high versus low grapefruit consumption, combining data for postmenopausal women from the two previously published studies with the data from the present study, there was no evidence of an association between grapefruit intake and risk of breast cancer (HR 1.06 (95% CI 0.95–1.19). However, these findings do not rule out the possibility of a small association between grapefruit consumption and breast cancer.

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