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Pre-diagnosis diet and survival after a diagnosis of ovarian cancer

Mary C Playdon[1], Christina M Nagle[2], Torukiri I Ibiebele[2], Leah M Ferrucci[1], Melinda M Protani[2,3], Jonathan Carter[4,5], Simon E Hyde[6], Deborah Neesham[7], James L Nicklin[8,9], Susan T Mayne[1,10,11] and Penelope M Webb*[,2,3] for the Australian Ovarian Cancer Study Group

[1]*Yale School of Public Health, Department of Chronic Disease Epidemiology, Yale University, 60 College Street, New Haven, CT 06520, USA;* [2]*Gynaecological Cancers Group, QIMR Berghofer Institute of Medical Research, 300 Herston Road, Herston, Queensland 4006, Australia;* [3]*School of Public Health, University of Queensland Public Health Building, Herston Road, Queensland 4006, Australia;* [4]*Department of Gynaecological Oncology, The University of Sydney, Sydney, New South Wales 2006, Australia;* [5]*Lifehouse Gynaecologic Oncology Group, Lifehouse, Royal Prince Alfred Hospital, Camperdown, New South Wales 2050, Australia;* [6]*Mercy Hospital for Women, Department of Gynaecological Oncology, Studley Road, Heidelberg, Victoria 3084, Australia;* [7]*Oncology/Dysplasia Unit, The Royal Women's Hospital, Flemington Road, Parkville, Victoria 3052, Australia;* [8]*Queensland Centre for Gynaecological Cancer, Royal Brisbane and Women's Hospital, Butterfield Street, Herston, Queensland 4029, Australia;* [9]*School of Medicine, Department of Obstetrics and Gynaecology, The University of Queensland, Herston, Queensland 4006, Australia;* [10]*Yale Cancer Center, New Haven, CT 06520, USA and* [11]*U.S. Food and Drug Administration, College Park, MD, USA*

Background: The relationship between diet and survival after ovarian cancer diagnosis is unclear as a result of a limited number of studies and inconsistent findings.

Methods: We examined the association between pre-diagnostic diet and overall survival in a population-based cohort ($n = 811$) of Australian women diagnosed with invasive epithelial ovarian cancer between 2002 and 2005. Diet was measured by validated food frequency questionnaire. Deaths were ascertained up to 31 August 2014 via medical record review and Australian National Death Index linkage. We conducted Cox proportional hazards regression analysis, controlling for diagnosis age, tumour stage, grade and subtype, residual disease, smoking status, body mass index, physical activity, marital status, and energy intake.

Results: We observed improved survival with highest compared with lowest quartile of fibre intake (hazard ratio (HR) = 0.69, 95% CI: 0.53–0.90, *P*-trend = 0.002). There was a suggestion of better survival for women with highest compared with lowest intake category of green leafy vegetables (HR = 0.79, 95% CI: 0.62–0.99), fish (HR = 0.74, 95% CI: 0.57–0.95), poly- to mono-unsaturated fat ratio (HR = 0.76, 95% CI: 0.59–0.98), and worse survival with higher glycaemic index (HR = 1.28, 95% CI: 1.01–1.65, *P*-trend = 0.03).

Conclusions: The associations we observed between healthy components of diet pre-diagnosis and ovarian cancer survival raise the possibility that dietary choices after diagnosis may improve survival.

Ovarian cancer has the highest mortality rate of all gynaecologic cancers (Hunn and Rodriguez, 2012), with the majority of women diagnosed at more advanced disease stages. Data from population-based registries have demonstrated that survival rates have not improved appreciably over time (Horner *et al*, 2009; Australian Institute of Health and Welfare, 2014). Lack of early screening tools and curative chemotherapy, as well as tumour molecular heterogeneity, are challenges to controlling the burden of disease

*Correspondence: Professor PM Webb; E-mail: penny.webb@qimrberghofer.edu.au

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(Hunn and Rodriguez, 2012). Observations that women with the same cancer characteristics given similar treatments can have different outcomes suggest there may be factors in addition to non-modifiable cancer characteristics that can influence survival (Bandera *et al*, 2009; Thomson and Alberts, 2010). Efforts to identify modifiable lifestyle factors that improve ovarian cancer survival have consequently gained momentum.

The mechanisms that drive ovarian carcinogenesis are not fully characterised, but may include elevated circulating gonadotropins, sex-steroid hormones, inflammatory cytokines, and altered glucose homeostasis (Ness and Modugno, 2006; Bandera *et al*, 2009; Wang and Sun, 2009; Yang *et al*, 2012). While diet has been shown to influence these mechanistic pathways and modify the carcinogenic process for other cancers (van Kruijsdijk *et al*, 2009; George *et al*, 2010), only five relatively large ($N = 244$–636) observational studies to our knowledge have explored the effects of diet on survival after ovarian cancer diagnosis and findings have been heterogeneous (Nagle *et al*, 2003; Zhang *et al*, 2004; Sakauchi *et al*, 2007; Dolecek *et al*, 2010; Thomson *et al*, 2014). Nonetheless, limited data indicate that diet may be associated with survival among women diagnosed with ovarian cancer, with some evidence of possible benefit from greater fruit and vegetable intake (Nagle *et al*, 2003; Dolecek *et al*, 2010), vitamin E (Nagle *et al*, 2003), green tea (Zhang *et al*, 2004), and overall diet quality (Thomson *et al*, 2014).

We agnostically explored the associations between 34 dietary exposures representing usual food, beverage, nutrient, and dietary supplement intake before diagnosis and overall survival in 811 women with invasive ovarian cancer who participated in the Australian Ovarian Cancer Study (AOCS), a nationwide case–control study.

MATERIALS AND METHODS

Australian ovarian cancer study. The AOCS has previously been described (Merritt *et al*, 2008). Briefly, women aged 18–79 years with a diagnosis of invasive or borderline epithelial ovarian, fallopian tube, or primary peritoneal cancer diagnosed between January 2002 and June 2006 were enrolled. The current analysis excluded women with borderline disease. Women were identified through gynaecologic oncology units and mandatory state-based cancer registries. Ethics approval and informed consent were obtained before enrolment. After exclusions (i.e., diagnosis not primary epithelial ovarian cancer or before study initiation, not an Australian resident), 1709 out of 2745 women agreed to participate; 1612 (94%) returned the main study questionnaire. Of these, 1132 women diagnosed with invasive disease before July 2005 also completed a food frequency questionnaire (FFQ). Women recruited in the final year of the study ($n = 242$) were not asked to complete the FFQ. After excluding participants who omitted 14 (10%) or more FFQ line items, those with implausible caloric intakes (<700 or >4000 kcal per day), and women who reported changing their diet over the 6–12 months before diagnosis because they were asked to report their diet before it changed ($n = 309$), dietary data were available for 811 women with invasive ovarian cancer.

Mortality ascertainment and follow-up. Vital status was determined through data abstracted from medical records every 6–12 months, and probabilistic record data linkage to the Australian National Death Index at the Australian Institute of Health and Welfare. All-cause mortality was the end point for follow-up, however, of those with cause of death information (90%, $n = 733$), 95% of deaths were attributed to ovarian cancer. Participants were followed for a mean of 5.9 ± 3.8 years. Survival time was defined as the interval between histologic diagnosis and date of death or censored at 31 August 2014. Left-truncated survival analyses were performed to account for the time elapsed between the date of diagnosis and study recruitment, in order to eliminate survivorship bias from excluding eligible women who died before study recruitment.

Covariates. Clinical data including International Federation of Obstetricians and Gynecologists stage (I/II and III/IV), tumour grade (well, moderately, or poorly differentiated, and missing), amount of residual tumour after surgery (none, $\leqslant 1$ cm, >1 cm, and missing), and histological subtype (serous, mucinous, endometrioid, clear cell, and other) were collected from histology reports and medical records. Socio-demographic and lifestyle information including age at diagnosis, education (school only, trade or technical qualification, and university), comorbid conditions including diabetes (none and $\geqslant 1$), smoking status (current, former, and never), height and weight (used to calculate body mass index (BMI): <18.5; 18.5–<25; 25–<30, and $\geqslant 30\,\mathrm{kg\,m^{-2}}$), amount of physical activity (low, medium, and high physical activity index (PAI)), and reproductive and hormonal data were obtained via self-administered questionnaire at study enrolment. Inclusion of a variable for the time elapsed between diagnosis and dietary assessment did not alter the effect estimates of interest so this was not included in the final models.

Dietary exposure assessment. Dietary intake was measured at recruitment via a semi-quantitative, 135-item FFQ adapted from that developed by Willett *et al* (1985, 1987; Ashton, 1996) and validated in an Australian population (McNaughton *et al*, 2005; Marks *et al*, 2006; Ibiebele *et al*, 2009). Questionnaires were completed a median of 3.3 months after diagnosis and intake was assessed for the year before diagnosis. Participants reported usual frequency of intake over the previous 12 months for standard serving sizes of food items and beverages. Frequency categories included '<1' or '1–3' times per month; '1', '2–4', or '5–6' times per week; and '1', '2–3', or '4+' times per day. Nutrient intake was estimated based on the Australian Food Composition Tables (Food Standards Australia New Zealand, 2010) and energy-adjusted using the residual method (Willett *et al*, 1997). Participants also reported type, quantity, and frequency of intake of dietary supplements. Nutrient intake from supplements was calculated by multiplying intake frequency by nutrient content given in the Australian Register of Therapeutic Goods (Therapeutic Goods Administration, 2013) following a process reported by Ashton *et al* (1997). Food group variables were calculated by summing the number of standard serving sizes consumed per day of relevant items in that group (items listed in Supplementary Table S1). Food group serving size categorisation was based on the distribution of intakes in the study population. Vegetable intake excluded potatoes. Dietary supplement use was categorised as either (1) non-user and user; or (2) non-user, <50th percentile of intake among users, and >50th percentile of intake among users, where data were available. Glycaemic index (GI) and glycaemic load (GL) were calculated using the Australian GI database (FoodWorks 2007, Xyris Software, Professional Edition, Highgate Hill, QLD, Australia) supplemented by the International Tables of Glycaemic Index and Glycaemic Load values (2008) (Atkinson *et al*, 2008). Dietary GL was calculated by multiplying grams of carbohydrate per food serving by the GI of that food.

Statistical analysis. Crude survival probabilities were estimated using the Kaplan–Meier technique. Associations between dietary factors and overall survival were estimated using Cox proportional hazards regression; multivariate hazard ratios (HRs) and 95% CIs were generated using SAS (SAS, version 9.3; SAS Institute, Cary, NC, USA). The underlying time-metric was person-time (months) of follow-up. A formal test for proportionality was conducted by modelling the interaction between the natural logarithm of follow-

up time and main dietary variables. Where the proportional hazards assumption was violated, a lag analysis was also conducted by stratifying the Cox proportional hazards models by different periods of follow-up time selected by inspecting the crude survival curves (Bellera *et al*, 2010). Effect estimates presented in tables are from models without the time interaction term.

A missing category was created for categorical variables with a large number of missing values. Variables associated with survival at $P<0.10$ in univariate models were evaluated in multivariate models. Stepwise backward selection was used to generate the most parsimonious models, retaining variables that improved model fit assessed by likelihood ratio test and remained statistically significant at $P<0.05$. Variables that were dropped from the model were added back in to multivariate models one at a time to confirm lack of effect on the estimates for each dietary exposure. The final multivariate models were adjusted for age at diagnosis, tumour stage and grade, amount of residual disease, subtype, smoking status, BMI, PAI, daily energy intake, and, where appropriate, marital status. Tests for linear trend were based on category median values. Finally, we conducted a sensitivity analysis, restricting to women diagnosed with high-grade (grade 3) serous tumours in order to determine diet–mortality associations within this homogenous subgroup.

RESULTS

Clinical, socio-demographic, and lifestyle characteristics of the 811 women included in this analysis are presented in Table 1. A total of 547 (67%) women died during follow-up, 5-year survival was 59.9% and median survival was 59.6 months. Serous histological subtype, later-stage disease, moderately or poorly differentiated tumour, greater residual disease, tumour originating in the peritoneum or fallopian tube, parity, lower educational attainment, not having a current partner, and having $\geqslant 1$ comorbid conditions were statistically significantly associated with worse survival in this cohort in univariate analyses.

Table 2 presents the associations between diet exposures and overall mortality. There was a trend for lower mortality with higher fruit intake (P-trend $=0.04$). Higher intake of green leafy vegetables was inversely associated with mortality (HR $=0.75$, 95% CI: 0.61, 0.93; HR $=0.79$, 95% CI: 0.62, 0.99 for increasing intake) although a linear trend was not evident (P-trend $=0.06$). A similar pattern was seen for fish intake (HR for $\geqslant 3$ *vs* 0 servings per day $=0.74$, 95% CI: 0.57, 0.95, P-trend $=0.17$). Cruciferous vegetable and low-fat dairy intake did not meet the proportional hazard assumption. In the lag analysis considering stages of follow-up time, cruciferous vegetable and low-fat dairy intake was not associated with mortality when restricting to $\leqslant$ or >3 years' follow-up time. Other food groups (grains, oily fish (tuna and salmon), total meat and meat subgroups (poultry, red meat, and processed meat), and low- and high-fat dairy) were not associated with mortality. For beverages including black and green tea, and coffee, we did not observe an association with mortality.

Table 3 presents the associations between nutrient intakes (second, third, and fourth *vs* first quartile) and overall mortality. Improved survival was evident for highest compared with lowest quartile of fibre intake (HR $=0.69$, 95% CI: 0.53, 0.90, P-trend $=0.002$) and worse survival with higher GI (HR $=1.28$, 95% CI: 1.01, 1.65, P-trend $=0.03$). Polyunsaturated to monounsaturated fat ratio (PUFA:MUFA) was associated with lower mortality for the highest compared with lowest quartile of intake (HR $=0.76$, 95% CI: 0.59, 0.98, P-trend $=0.06$). There was a suggestive trend for increasing risk of mortality with higher intakes of saturated fat ($P=0.07$). No association was observed between total vitamin C, E, β-carotene, and retinol from diet plus supplements, total fat, mono or polyunsaturated fat alone, or GL and mortality.

Table 4 presents associations between dietary supplement use and overall mortality. The interaction of vitamin C intake from supplements with survival time was statistically significant. Above median intake of vitamin C (180 mg per day) from supplements was positively associated with mortality during the first 5 years after diagnosis (HR *vs* no use $=1.36$, 95% CI: 1.04, 1.78) but was not associated with mortality after 5 years. Among vitamin C supplement users, the range of intake was up to 2039 mg per day (IQR: 74–500).

We analysed 34 diet–mortality associations; adjusting for multiple comparisons would result in significant associations at a false discovery rate set at 0.2 of <0.006 (0.2/(34/1)) for the highest-ranked P-value. Thus, taking this into consideration, the inverse association between fibre and mortality remained statistically significant for this agnostic analysis.

Similar patterns were seen in sensitivity analyses restricted to women with high-grade serous tumours however the associations tended to be slightly stronger. As a result the inverse associations with total vegetable, oily fish, and green tea intake, and the positive association with total fat intake reached statistical significance (Supplementary Tables S2–S4). A significant inverse trend was also seen for cruciferous vegetables and a significant positive trend for coffee intake although none of the individual category estimates reached statistical significance.

DISCUSSION

Our findings from a large, Australian population-based sample of women diagnosed with invasive epithelial ovarian cancer support a possible association between pre-diagnostic diet and survival after diagnosis. Overall, we observed a survival advantage for higher intakes of total and green leafy vegetables, fruit, fish, fibre intake, and PUFA:MUFA ratio, while higher GI was associated with worse survival. Higher vitamin C intake from supplements was inversely associated with survival up to 5 years after diagnosis but not after 5 years. A significant dose–response relationship (for survival advantage) was observed for both increasing fibre intake (better survival) and GI (worse survival). After controlling for multiple comparisons, the association with fibre remained statistically significant. Our findings were independent of tumour characteristics and, when we restricted to high-grade serous cases, the associations remained and we also observed a trend for reduced mortality risk with higher cruciferous vegetable and green tea intakes. These findings expand on a limited area of research as, to our knowledge, only five studies have been conducted on dietary exposures and survival after ovarian cancer diagnosis (Nagle *et al*, 2003; Zhang *et al*, 2004; Sakauchi *et al*, 2007; Yang *et al*, 2008; Dolecek *et al*, 2010; Thomson *et al*, 2014).

The World Cancer Research Fund Continuous Update Project Report on diet and risk of ovarian cancer judged the evidence that diet has a role as only limited/suggestive due to the scarcity and/or inconsistency of findings to date (World Cancer Research Fund/American Institute for Cancer Research, 2014). Nonetheless, emerging evidence supports some associations between diet and ovarian cancer survival. Findings from the Women's Health Initiative ($N=636$ ovarian cancer cases) found significantly lower all-cause mortality for women reporting higher pre-diagnosis diet quality as measured by the Healthy Eating Index–2005, but no significant associations with the individual dietary components contributing to the dietary score (Thomson *et al*, 2014). It is possible that overall pattern of food consumption that accounts for correlated intakes and food/nutrient interactions is a more important exposure in the context of ovarian cancer as opposed

Table 1. Clinical, socio-demographic, and lifestyle characteristics and associations with all-cause mortality among women diagnosed with invasive ovarian cancer participating in the AOCS ($n = 811$)

Characteristics	N (%)[a]	Deceased (%)	Univariate HR (95% CI)[b]
Age at diagnosis			
<50 years	148 (18)	49	1.00 (ref)
50–59 years	269 (33)	64	1.47 (1.12, 1.94)
60–69 years	250 (31)	75	1.92 (1.46, 2.52)
⩾70 years	144 (18)	81	2.49 (1.86, 3.35)
Histological subtype			
Serous	536 (66)	79	1.00 (ref)
Mucinous	30 (4)	33	0.27 (0.15, 0.51)
Endometrioid	88 (11)	31	0.25 (0.17, 0.37)
Clear cell	54 (7)	44	0.42 (0.28, 0.64)
Other	103 (13)	63	0.73 (0.56, 0.95)
Stage			
I/II	234 (29)	30	1.00 (ref)
III/IV	571 (71)	82	4.93 (3.83, 6.34)
Grade			
Well differentiated	76 (9)	41	1.00 (ref)
Moderately differentiated	156 (19)	69	2.27 (1.52, 3.39)
Poorly differentiated	530 (65)	72	2.46 (1.71, 3.56)
Missing	49 (6)	55	1.61 (0.96, 2.70)
Residual disease			
No residual	328 (40)	42	1.00 (ref)
⩽1 cm	181 (22)	85	3.46 (2.75, 4.37)
>1 cm	185 (23)	91	4.53 (3.60, 5.70)
Missing	117 (14)	74	2.36 (1.80, 3.08)
Ovarian cancer site			
Ovary	703 (87)	66	1.00 (ref)
Peritoneum/fallopian tube	108 (13)	78	1.38 (1.09, 1.74)
Hormone therapy use			
No	484 (60)	64	1.00 (ref)
Yes	320 (39)	73	1.14 (0.96, 1.35)
Parity			
None	143 (18)	53	1.00 (ref)
1–2 pregnancies	343 (42)	66	1.41 (1.09, 1.83)
⩾3 pregnancies	323 (40)	75	1.69 (1.30, 2.19)
Body mass index (kg m^{-2})			
<18.5 (underweight)	40 (5)	70	1.07 (0.72, 1.58)
18.5–<25 (normal weight)	382 (47)	68	1.00 (ref)
25–<30 (overweight)	239 (29)	67	0.88 (0.73, 1.08)
⩾30 (obese)	141 (17)	66	0.92 (0.73, 1.17)
Physical activity index			
Low	176 (22)	73	1.00 (ref)
Medium	295 (36)	66	0.83 (0.67, 1.03)
High	339 (42)	66	0.81 (0.65, 1.02)
Education			
School only	440 (54)	74	1.00 (ref)
Trade or technical	257 (32)	61	0.74 (0.62, 0.90)
University	114 (14)	59	0.73 (0.56, 0.95)
Marital status			
Current partner	591 (73)	66	1.00 (ref)
Ex-partner/never married	218 (27)	72	1.25 (1.04, 1.50)
Number of comorbidities			
None	621 (77)	65	1.00 (ref)
⩾1	187 (23)	76	1.35 (1.11, 1.63)
Current smoker (1 year before diagnosis)			
Never	488 (60)	69	1.00 (ref)
Former	209 (26)	63	0.86 (0.70, 1.05)
Current	114 (14)	68	1.00 (0.78, 1.29)
Vital status			
Alive	264 (33)		
Deceased	547 (67)		

Abbreviations: AOCS = Australian Ovarian Cancer Study; CI = confidence interval; HR = hazard ratio; ref = reference.
[a]Percentages may not sum to 100% due to rounding.
[b]Cox proportional hazards regression.

to the role of single foods or nutrients. A large-scale prospective cohort study in Japan ($N = 64\,327$ women) assessed baseline frequency of intake of 32 food items and followed women for an average of 13 years; 77 women died of ovarian cancer. Salted fish and pickled Chinese cabbage were positively associated with ovarian cancer mortality but no other dietary associations were observed (Sakauchi *et al*, 2007). As survival was not the focus of this cohort, it is unclear how these dietary exposures were associated with ovarian cancer incidence and subsequent survival. A longitudinal study of 341women enrolled in a United States (US) case–control study between 1994 and 1998 found better survival for women with higher intake of fruits plus vegetables, total vegetables, and yellow and cruciferous vegetables pre-diagnosis (Dolecek *et al*, 2010). They also observed poorer survival with higher intakes of red and cured meats, and milk. Those findings were generally supported by another Australian study of 609 women diagnosed between 1990 and 1993, where better survival was observed with higher pre-diagnosis intakes of vegetables, cruciferous vegetables, and vitamin E, whereas lactose, dairy products, protein, red meat, and white meat were associated with worse survival (Nagle *et al*, 2003).

Some of these associations for individual foods were not observed in our current population; however, there are a number of differences between the studies. Compared with the current analysis, the US sample was slightly younger with earlier disease at diagnosis. Dietary intake was reported for the 3- to 5-year period before diagnosis as opposed to 12 months in this study, and the previous Australian study (Nagle *et al*, 2003; Dolecek *et al*, 2010). Similarly, participants in the first Australian study were younger with earlier-stage disease (Nagle *et al*, 2003). However, when we restricted analyses to participants aged <50 years, results were not altered significantly with regards to these dietary components. As cases in the current study were diagnosed 10 years after the first Australian study, changes in food consumption patterns could have influenced heterogeneity of exposure (Flood *et al*, 2010; Arabshahi *et al*, 2011), although intakes appeared similar to those in the previous study.

We observed an inverse association between green leafy vegetables (spinach and lettuces) and mortality, and a trend for reduced mortality risk with higher fruit intake. Spinach is rich in beta-carotene, lutein/zeaxanthin, and other vitamins and minerals. While two population-based case–control studies have reported reduced risks of ovarian cancer for the highest compared with lowest intakes of lutein/zeaxanthin (Bertone *et al*, 2001), two prospective cohorts found no association between green leafy vegetable intake and incident epithelial ovarian cancer (Larsson *et al*, 2004; Schulz *et al*, 2005). A previous analysis reported an inverse association between pre-diagnosis intake of fruit and vegetables combined and ovarian cancer survival (Dolecek *et al*, 2010), but analyses of diet and survival after diagnosis of ovarian cancer to date have grouped spinach/lettuce intake with total vegetable intake (Nagle *et al*, 2003; Dolecek *et al*, 2010). In addition to fibre, green leafy vegetables are also a good source of other nutrients shown to be implicated in cancer aetiology, including folate and flavonoids, although evidence for their roles in ovarian cancer survival is sparse (Zhang *et al*, 2004; Dixon *et al*, 2014).

For total fish intake, we observed a protective association with survival, but no dose–response relationship. In two Australian case–control studies, higher fish intake was associated with lower risk (Kolahdooz *et al*, 2010) but a meta-analysis of 15 case–control and cohort studies found that total fish consumption was not associated with ovarian cancer risk overall, although it was protective in Australian/European but not in Asian/North American studies (Jiang *et al*, 2014). Mechanisms proposed to explain the protective effect of fish intake include the rich source of omega-3 fatty acids and their anti-apoptotic and anti-

Table 2. Association between pre-diagnosis food and beverage intake and overall mortality among women diagnosed with invasive ovarian cancer participating in the AOCS ($n = 811$)

Dietary variable	*N* (%)	Deaths, *N* (%)	Age and energy-adjusted HR (95% CI)	Multivariate HR (95% CI)[a]	Multivariate *P*-trend[b]
Fruit (servings per day)					
None or <2	206 (25)	141 (26)	1.00 (ref)	1.00 (ref)	0.04
2–<4	275 (34)	187 (34)	0.83 (0.66, 1.03)	0.91 (0.72, 1.16)	
⩾4	330 (41)	219 (40)	0.78 (0.61, 0.99)	0.82 (0.63, 1.07)	
Total vegetables (servings per day)					
None or <3	213 (26)	143 (26)	1.00 (ref)	1.00 (ref)	0.48
3–<5	331 (41)	221 (40)	0.90 (0.72, 1.11)	0.95 (0.76, 1.18)	
⩾5	267 (33)	183 (33)	0.93 (0.73, 1.19)	0.88 (0.68, 1.13)	
Green leafy vegetables (servings per day)					
None or <0.33	255 (31)	173 (32)	1.00 (ref)	1.00 (ref)	0.06
0.33–<0.67	311 (38)	210 (38)	0.92 (0.76, 1.13)	0.75 (0.61, 0.93)	
⩾0.67	245 (30)	164 (30)	0.94 (0.76, 1.18)	0.79 (0.62, 0.99)	
Cruciferous vegetables (servings per day)					
None or <0.75	425 (52)	287 (52)	1.00 (ref)	1.00 (ref)	0.66[c]
0.75–<1.5	257 (32)	169 (31)	0.87 (0.72, 1.06)	0.90 (0.74, 1.10)	
⩾1.5	129 (16)	91 (17)	1.03 (0.81, 1.31)	0.99 (0.77, 1.29)	
Red/yellow vegetables (servings per day)					
None or <1	219 (27)	145 (27)	1.00 (ref)	1.00 (ref)	0.40[d]
1–<2	407 (50)	279 (51)	0.95 (0.78, 1.17)	0.92 (0.74, 1.14)	
⩾2	185 (23)	123 (22)	0.90 (0.69, 1.18)	0.91 (0.69, 1.20)	
Grains (servings per day)					
None or <2	227 (28)	140 (26)	1.00 (ref)	1.00 (ref)	0.75
2–<4	367 (45)	253 (46)	1.23 (0.99, 1.53)	1.12 (0.89, 1.40)	
⩾4	217 (27)	154 (28)	1.18 (0.91, 1.52)	1.11 (0.85, 1.45)	
Total meat (servings per day)					
None or <1	268 (33)	172 (31)	1.00 (ref)	1.00 (ref)	0.43
1–<2	424 (52)	298 (54)	1.22 (1.00, 1.49)	1.14 (0.95, 1.43)	
⩾2	119 (15)	77 (14)	1.18 (0.87, 1.60)	0.98 (0.71, 1.35)	
Poultry (servings per week)					
None or <1	280 (35)	192 (35)	1.00 (ref)	1.00 (ref)	0.82
1–<2	150 (19)	103 (19)	1.05 (0.82, 1.33)	1.03 (0.80, 1.32)	
⩾2	380 (47)	251 (46)	1.02 (0.84, 1.24)	0.98 (0.80, 1.20)	
Processed meat (servings per week)					
None or <1	314 (39)	211 (39)	1.00 (ref)	1.00 (ref)	0.81
1–<2	221 (27)	155 (28)	1.13 (0.92, 1.39)	1.25 (1.00, 1.55)	
⩾2	276 (34)	181 (33)	1.08 (0.88, 1.33)	1.08 (0.86, 1.35)	
Red meat (servings per week)					
None or <2	126 (16)	77 (14)	1.00 (ref)	1.00 (ref)	0.44
2–<4	220 (27)	151 (28)	1.22 (0.92, 1.61)	1.28 (0.96, 1.71)	
4–<6	214 (26)	143 (26)	1.20 (0.91, 1.60)	1.18 (0.88, 1.58)	
⩾6	251 (31)	176 (32)	1.32 (0.98, 1.76)	1.21 (0.89, 1.64)	
Total fish (servings per week)					
None or <1	183 (23)	132 (24)	1.00 (ref)	1.00 (ref)	0.17[d]
1–<2	229 (28)	154 (28)	0.86 (0.68, 1.08)	0.70 (0.55, 0.89)	
2–<3	142 (18)	98 (18)	0.95 (0.73, 1.24)	0.76 (0.58, 1.00)	
⩾3	257 (32)	163 (30)	0.85 (0.67, 1.08)	0.74 (0.57, 0.95)	
Oily fish (servings per week)					
None	103 (13)	76 (14)	1.00 (ref)	1.00 (ref)	0.71
<1	402 (50)	270 (49)	0.77 (0.60, 1.00)	0.61 (0.47, 0.80)	
<1–2	156 (19)	106 (19)	0.81 (0.60, 1.08)	0.61 (0.45, 0.84)	
⩾2	150 (19)	95 (17)	0.80 (0.59, 1.09)	0.80 (0.58, 1.11)	
Low-fat dairy (servings per day)					
None	141 (17)	102 (19)	1.00 (ref)	1.00 (ref)	0.68[c]
>0–1	331 (41)	222 (41)	0.88 (0.69, 1.11)	0.81 (0.64, 1.04)	
>1–2	199 (25)	128 (23)	0.79 (0.61, 1.02)	0.79 (0.59, 1.04)	
>2	139 (17)	94 (17)	0.90 (0.67, 1.19)	0.98 (0.73, 1.33)	
High-fat dairy (servings per day)					
None or ⩽1	361 (45)	238 (44)	1.00 (ref)	1.00 (ref)	0.32
>1–2	283 (35)	195 (36)	1.00 (0.82, 1.22)	1.15 (0.94, 1.42)	
>2	167 (21)	114 (21)	1.12 (0.88, 1.42)	1.11 (0.87, 1.42)	
Coffee (250 ml mugs per day)					
None	156 (19)	105 (19)	1.00 (ref)	1.00 (ref)	0.86[d]
⩽1	303 (37)	204 (37)	0.89 (0.70, 1.13)	0.86 (0.67, 1.10)	
>1–⩽2	90 (11)	62 (11)	1.13 (0.83, 1.55)	1.14 (0.82, 1.57)	
>2–⩽3	183 (23)	130 (24)	1.08 (0.84, 1.40)	1.03 (0.79, 1.35)	
>3	79 (10)	46 (8)	0.79 (0.56, 1.12)	0.83 (0.58, 1.19)	

Table 2. (Continued)

Dietary variable	*N* (%)	Deaths, *N* (%)	Age and energy-adjusted HR (95% CI)	Multivariate HR (95% CI)[a]	Multivariate *P*-trend[b]
Black tea (250 ml mugs per day)					
None	135 (17)	91 (17)	1.00 (ref)	1.00 (ref)	0.73[d]
<1	168 (21)	96 (18)	0.78 (0.58, 1.04)	0.78 (0.59, 1.06)	
1–<2	113 (14)	81 (15)	1.13 (0.84, 1.53)	0.94 (0.69, 1.29)	
2–<3	274 (34)	195 (36)	1.00 (0.78, 1.29)	0.97 (0.74, 1.25)	
⩾3	121 (15)	84 (15)	0.89 (0.66, 1.21)	0.78 (0.59, 1.06)	
Green tea (250 ml mugs per day)					
Non-drinker	545 (67)	372 (68)	1.00 (ref)	1.00 (ref)	0.28
<1	194 (24)	128 (23)	0.96 (0.78, 1.17)	0.92 (0.75, 1.13)	
⩾1	72 (9)	47 (9)	0.90 (0.66, 1.21)	0.83 (0.60, 1.15)	

Abbreviations: AOCS = Australian Ovarian Cancer Study; CI = confidence interval; HR = hazard ratio; ref = reference.
[a]Cox proportional hazards regression, adjusted for age at diagnosis, International Federation of Gynaecology and Obstetrics (FIGO) stage, amount of residual disease, grade, tumour subtype, smoking status, body mass index, physical activity index, marital status, and daily caloric intake.
[b]*P*-value for linear trend calculated from category median values.
[c]Proportional hazards assumption not met; time–variable interaction statistically significant in multivariate model. Original hazard ratio (95% CI) without time–variable interaction included in the model is presented.
[d]Not adjusted for marital status.

inflammatory properties (Fernandez *et al*, 1999; Sharma *et al*, 2005). Fish has not previously been analysed independently of other white meats in relation to ovarian cancer survival (Nagle *et al*, 2003; Dolecek *et al*, 2010).

We observed a beneficial effect of dietary fibre, which lowers circulating oestrogens by inhibiting bile reabsorption and increasing faecal excretion (Ferrari *et al*, 2013), on survival. In the previous Australian analysis, fibre was not associated with ovarian cancer survival (Nagle *et al*, 2003), although the median of the highest-intake category was lower than the current analysis (35 *vs* 43 g per day). We found a similarly null association for fibre intake of 35 g per day, suggesting a protective effect only for particularly high levels of fibre intake. To date, no other studies have explored this association. Findings for the association between fibre intake and ovarian cancer risk have been mixed (Silvera *et al*, 2007a; Hedelin *et al*, 2011), although fibre intake has been associated with lower breast cancer mortality (Belle *et al*, 2011; Buck *et al*, 2011). A high-fibre, low-fat dietary intervention was shown to reduce bioavailable oestrogen among women diagnosed with breast cancer, a plausible mechanism in the context of improving ovarian cancer survival (Rock *et al*, 2004). Other potential mechanisms for fibre's inverse association with mortality include its influence on inflammation (Ma *et al*, 2008; Villasenor *et al*, 2011), and metabolic regulation including effects on GI (Lattimer and Haub, 2010).

We found suggestive evidence for a trend towards poorer survival with increasing saturated fat intake, which has not been observed in prior studies (Nagle *et al*, 2003; Dolecek *et al*, 2010). High dietary fat intake has been proposed to increase circulating progesterone and oestrogens, promoting tumour development (Pyragius *et al*, 2013). Previous investigations highlight the inconsistency of this association (Genkinger *et al*, 2006; Blank *et al*, 2012).

The ratio of PUFA:MUFA was inversely associated with mortality. PUFA, largely found in nuts, seeds, fish, and leafy green vegetables, includes both omega-3 (n-3) and omega-6 (n-6) subtypes; avocado, canola, and olive oils are good sources of MUFA. A large population-based case–control study ($n = 1872$ cases and 1978 controls) found a lower risk of epithelial ovarian cancer for the highest compared with lowest intakes of overall PUFA, n-3 and n-6 PUFA, but no association with MUFA (Merritt *et al*, 2014). The ratio of PUFA:MUFA was not associated with risk for developing ovarian cancer in a second study (Ibiebele *et al*, 2012). Unsaturated fatty acids have a role in cell membrane integrity and can affect cell function through eicosanoid synthesis, gene expression regulation, and effects on apoptosis and cell proliferation (Abel *et al*, 2014). Previous studies have shown that n-3 FA inhibit ovarian cancer cell proliferation (Sharma *et al*, 2005; Sharma *et al*, 2009), but the importance of n-6:n-3 and PUFA:MUFA in the context of carcinogenesis remains unclear (Abel *et al*, 2014). Prior studies of diet and ovarian cancer survival have not assessed unsaturated fatty acid ratio (Nagle *et al*, 2003; Zhang *et al*, 2004; Sakauchi *et al*, 2007; Yang *et al*, 2008; Dolecek *et al*, 2010).

GI showed a positive linear relationship with mortality. Previous case–control and prospective cohort studies have reported mixed findings for the association between GI and ovarian cancer risk (Augustin *et al*, 2003; Silvera *et al*, 2007b; George *et al*, 2009; Nagle *et al*, 2011). The GI quantitatively assesses the effect of food on post-consumption blood glucose levels and is purported to influence carcinogenesis by increasing circulating insulin-like growth factors and oestrogens, and promoting tumour progression through insulin-related cell signalling (George *et al*, 2009). Studies on ovarian cancer survival are lacking.

Vitamin C supplement intake was positively associated with mortality for the earlier period of follow-up (up to 5 years) but we found no association with vitamin C from diet alone. Previous investigations on ovarian cancer survival have not reported on supplemental vitamin C and findings for the association with ovarian cancer risk have been mixed (Fleischauer *et al*, 2001; Chang *et al*, 2008; Crane *et al*, 2014; Koushik *et al*, 2015). A null association between vitamin C from food and ovarian cancer risk but a harmful effect for vitamin C supplement use has also been reported (Gifkins *et al*, 2012). Findings from the WHI among vitamin C replete postmenopausal women also showed that women who went on to develop ovarian cancer had significantly higher vitamin C supplement intake than controls. Proposed mechanisms included vitamin C pro-oxidant activity and enhanced iron absorption with iron-associated oxidative stress and effects on malignant transformation (Thomson *et al*, 2008). Future studies powered to explore dietary supplement intake and ovarian cancer survival with characterisation of dose, formulation, and duration are warranted.

Our study has several strengths, including its large sample size, long duration and complete follow-up, population-based case selection and detailed collection of information on tumour characteristics, and lifestyle factors, allowing adjustment for known prognostic factors. There was comprehensive measurement of food, nutrient, and dietary supplement exposures. Some limitations should be addressed. Diet was measured pre-diagnosis and may not reflect intake after diagnosis. Nevertheless, although some women may change their diet after cancer diagnosis, overall, pre-diagnosis diet is likely to be correlated with post-diagnosis diet. Studies of breast cancer survivors suggest dietary changes after

Table 3. Association between nutrient intake from foods and supplements pre-diagnosis and overall mortality among women diagnosed with invasive ovarian cancer participating in the AOCS ($n = 811$)

	Quartile[a]				
Nutrient	**1**	**2**	**3**	**4**	***P*-trend[b]**
Fibre (g per day)					
Deaths, *N* (% of total deaths)	129 (24)	143 (26)	144 (26)	131 (24)	0.002
Median	23	30	35	43	
Age-/E-adjusted HR (95% CI)	1.00 (ref)	1.06 (0.83, 1.35)	0.95 (0.75, 1.21)	0.86 (0.67, 1.10)	
Multivariate HR (95% CI)	1.00 (ref)	1.03 (0.80, 1.32)	0.89 (0.69, 1.14)	0.69 (0.53, 0.90)	
Vitamin C (diet only; mg per day)					
Deaths, *N* (% of total deaths)	139 (25)	136 (25)	135 (25)	137 (25)	0.53[c]
Median	112	158	200	276	
Age-/E-adjusted HR (95% CI)	1.00 (ref)	0.92 (0.73, 1.16)	0.91 (0.72, 1.16)	0.88 (0.69, 1.11)	
Multivariate HR (95% CI)	1.00 (ref)	1.01 (0.79, 1.30)	1.06 (0.82, 1.36)	0.93 (0.72, 1.19)	
Vitamin C (diet and supplements; mg per day)					
Deaths, *N* (% of total deaths)	139 (25)	144 (26)	139 (25)	125 (23)	0.82
Median	124	183	257	532	
Age-/E-adjusted HR (95% CI)	1.00 (ref)	1.03 (0.82, 1.31)	0.97 (0.77, 1.23)	0.91 (0.71, 1.16)	
Multivariate HR (95% CI)	1.00 (ref)	1.18 (0.93, 1.50)	1.11 (0.87, 1.42)	1.04 (0.81, 1.35)	
Vitamin E (diet and supplements; mg per day)					
Deaths, *N* (% of total deaths)	138 (25)	144 (26)	133 (24)	132 (24)	0.23
Median	6	8	10	40	
Age-/E-adjusted HR (95% CI)	1.00 (ref)	0.99 (0.78, 1.25)	0.88 (0.69, 1.11)	0.98 (0.77, 1.25)	
Multivariate HR (95% CI)	1.00 (ref)	0.94 (0.74, 1.20)	0.85 (0.66, 1.09)	1.07 (0.83, 1.37)	
Beta-carotene (diet and supplements; μg per day)					
Deaths, *N* (% of total deaths)	135 (25)	146 (27)	134 (25)	132 (24)	0.44
Median	2909	4757	6310	9183	
Age-/E-adjusted HR (95% CI)	1.00 (ref)	0.97 (0.77, 1.23)	0.88 (0.69, 1.11)	0.85 (0.67, 1.08)	
Multivariate HR (95% CI)	1.00 (ref)	0.93 (0.73, 1.19)	1.05 (0.82, 1.35)	0.89 (0.69, 1.14)	
Retinol (diet and supplements; μg per day)					
Deaths, *N* (% of total deaths)	131 (24)	147 (27)	135 (25)	134 (25)	0.57
Median	183	290	526	1433	
Age-/E-adjusted HR (95% CI)	1.00 (ref)	1.16 (0.92, 1.47)	0.96 (0.75, 1.22)	0.93 (0.73, 1.19)	
Multivariate HR (95% CI)	1.00 (ref)	1.27 (1.00, 1.63)	1.10 (0.85, 1.41)	1.05 (0.81, 1.34)	
Total fat (g per day)					
Deaths, *N* (% of total deaths)	137 (25)	137 (25)	138 (25)	135 (25)	0.27[c]
Median	57	68	76	86	
Age-/E-adjusted HR (95% CI)	1.00 (ref)	1.07 (0.84, 1.35)	1.04 (0.82, 1.32)	1.12 (0.88, 1.42)	
Multivariate HR (95% CI)	1.00 (ref)	1.28 (1.00, 1.64)	1.12 (0.87, 1.42)	1.19 (0.92, 1.53)	
Monounsaturated fat (g per day)					
Deaths, *N* (% of total deaths)	131 (24)	143 (26)	141 (26)	132 (24)	0.55
Median	20	24	27	32	
Age-/E-adjusted HR (95% CI)	1.00 (ref)	1.28 (1.01, 1.62)	1.23 (0.97, 1.56)	1.10 (0.87, 1.40)	
Multivariate HR (95% CI)	1.00 (ref)	1.31 (1.03, 1.67)	1.26 (0.98, 1.61)	1.09 (0.85, 1.41)	
Polyunsaturated fat (g per day)					
Deaths, *N* (% of total deaths)	132 (24)	143 (26)	146 (27)	126 (23)	0.46
Median	9	11	13	16	
Age-/E-adjusted HR (95% CI)	1.00 (ref)	1.14 (0.90, 1.45)	1.15 (0.91, 1.45)	0.93 (0.73, 1.19)	
Multivariate HR (95% CI)	1.00 (ref)	0.94 (0.74, 1.20)	1.01 (0.79, 1.30)	0.89 (0.69, 1.15)	
Saturated fat (g per day)					
Deaths, *N* (% of total deaths)	134 (25)	136 (25)	138 (25)	139 (25)	0.07[c]
Median	19	25	29	35	
Age-/E-adjusted HR (95% CI)	1.00 (ref)	1.03 (0.81, 1.31)	1.11 (0.88, 1.41)	1.17 (0.92, 1.48)	
Multivariate HR (95% CI)	1.00 (ref)	1.12 (0.87, 1.43)	1.30 (1.02, 1.67)	1.23 (0.96, 1.58)	
PUFA:MUFA					
Deaths, *N* (% of total deaths)	136 (25)	136 (25)	144 (26)	131 (24)	0.06
Median	0.36	0.43	0.49	0.59	
Age-/E-adjusted HR (95% CI)	1.00 (ref)	0.92 (0.73, 1.17)	0.94 (0.74, 1.19)	0.82 (0.64, 1.04)	
Multivariate HR (95% CI)	1.00 (ref)	0.82 (0.64, 1.05)	0.85 (0.66, 1.08)	0.76 (0.59, 0.98)	
Glycaemic index					
Deaths, *N* (% of total deaths)	128 (23)	133 (24)	136 (25)	150 (27)	0.03[c]
Median	45	48.5	51.4	55.1	
Age-/E-adjusted HR (95% CI)	1.00 (ref)	1.03 (0.81, 1.31)	1.11 (0.87, 1.41)	1.30 (1.03, 1.65)	
Multivariate HR (95% CI)	1.00 (ref)	1.07 (0.83, 1.37)	1.13 (0.88, 1.45)	1.28 (1.01, 1.65)	

Table 3. (Continued)

Nutrient	Quartile[a] 1	2	3	4	*P*-trend[b]
Glycaemic load					
Deaths, *N* (% of total deaths)	127 (23)	134 (25)	147 (27)	139 (25)	0.28[c]
Median	93	111	125	142	
Age-/E-adjusted HR (95% CI)	1.00 (ref)	0.99 (0.78, 1.26)	1.23 (0.97, 1.56)	1.08 (0.85, 1.38)	
Multivariate HR (95% CI)	1.00 (ref)	1.07 (0.83, 1.38)	1.22 (0.95, 1.57)	1.12 (0.87, 1.44)	

Abbreviations: AOCS = Australian Ovarian Cancer Study; CI = confidence interval; E = energy; HR = hazard ratio; MUFA = monounsaturated fat; PUFA = polyunsaturated fat; ref = reference.
[a]Cox proportional hazards regression, adjusted for age at diagnosis, International Federation of Gynaecology and Obstetrics (FIGO) stage, amount of residual disease, grade, tumour subtype, smoking status, body mass index, physical activity index, and daily caloric intake.
[b]*P*-value for linear trend calculated from category median values.
[c]Additionally adjusted for marital status.

Table 4. Association between dietary supplement intake pre-diagnosis and overall mortality among women diagnosed with invasive ovarian cancer participating in the AOCS ($n = 811$)

Supplement	*N* (%)	Deaths, *N* (%)	Age and energy-adjusted HR (95% CI)	Multivariate HR (95% CI)[a]	*P*-value
Takes multivitamin supplements					
No	618 (76)	421 (77)	1.00 (ref)	1.00 (ref)	0.16
Yes	192 (24)	125 (23)	1.14 (1.93, 1.40)	1.16 (0.94, 1.43)	
Takes vitamin B supplements					
No	697 (86)	471 (89)	1.00 (ref)	1.00 (ref)	0.30[b]
Yes	88 (11)	60 (11)	1.00 (0.76, 1.33)	1.16 (0.88, 1.53)	
Total vitamin C from supplements[c]					
None	542 (67)	377 (69)	1.00 (ref)	1.00 (ref)	0.74[d]
⩽180 mg per day	131 (16)	84 (10)	1.11 (0.87, 1.41)	1.20 (0.93, 1.54)	
>180 mg per day	138 (17)	86 (16)	0.96 (0.76, 1.21)	1.05 (0.82, 1.35)	
Total vitamin E from supplements[c]					
None	618 (76)	421 (77)	1.00 (ref)	1.00 (ref)	0.14
⩽30 mg per day	91 (11)	56 (10)	1.06 (0.80, 1.41)	1.12 (0.84, 1.50)	
>30 mg per day	102 (13)	70 (13)	1.11 (0.86, 1.43)	1.22 (0.94, 1.59)	

Abbreviations: AOCS = Australian Ovarian Cancer Study; CI = confidence interval; HR = hazard ratio; ref = reference.
[a]Cox proportional hazards regression, adjusted for age at diagnosis, International Federation of Gynaecology and Obstetrics (FIGO) stage, amount of residual disease, grade, tumour subtype, smoking status, body mass index, physical activity index, and daily caloric intake.
[b]Additionally adjusted for marital status.
[c]Dose categories are based on nutrients present in individual supplements plus nutrients from multivitamin supplements.
[d]Proportional hazards assumption not met; time–variable interaction statistically significant in multivariate model. Original hazard ratio (95% CI) without time–variable interaction included in the model is presented.

diagnosis are modest (Wayne *et al*, 2004), and limited post-diagnosis dietary data available for 289 women in our cohort showed moderate correlations for fruit, vegetables, and meat (intraclass correlations 0.46, 0.32, and 0.42, respectively). Furthermore, we restricted the current analysis to women who reported no change in their diet for the 6–12 months before diagnosis. There is the potential for selection bias if the association between diet and survival differs by characteristics of participants compared with non-participants, given that enrolment was limited to those well enough to complete dietary assessment. However, this cohort included women who diagnosed primarily with later-stage disease, reflecting the general population of ovarian cancer survivors. Information or recall bias is a possible limitation as diagnosis of late-stage disease with reduced wellbeing may have influenced dietary recall, although our results were adjusted for stage and grade of disease, and we observed similar associations by disease stage. Any measurement error, inherent in self-report measures for dietary assessment, is likely to have attenuated real associations and thus cannot explain the associations seen. Given the observational design, it is possible that observed associations are due to confounding by unknown or unmeasured confounding factors although we adjusted for the key factors known to influence ovarian cancer survival. Results may be due to chance; after controlling for multiple comparisons, only fibre remained statistically significantly inversely associated with mortality.

In summary, in one of few dietary analyses within a large, observational study of women diagnosed with invasive ovarian cancer, we observed improved survival with higher intakes of dietary fibre. There was a suggestion of improved survival with higher consumption of green leafy vegetables, fish, and PUFA:-MUFA ratio, and poorer survival with higher GI that require replication in future large-scale prospective studies. These observations that healthy components of a pre-diagnosis diet are associated with ovarian cancer survival raise the possibility that healthful dietary choices after diagnosis may improve ovarian cancer survival. The role of diet in ovarian cancer survival would be further clarified by analyses of post-diagnosis diet, evidence for which is currently being gathered in a randomised, controlled (Thomson *et al*, 2016).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

MCP conducted statistical analysis and wrote the paper; CMN contributed to study design and statistical analysis; TII was responsible for the dietary data and estimation of nutrient intakes; MMP conducted the linkage to the National Death Index; JC, SH, DN, and JN contributed to participant recruitment and data collection; LMF and STM contributed to statistical analysis; and PMW designed the study and has primary responsibility for the final content. All authors reviewed and approved the final manuscript.

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