The Dietary Inflammatory Index: A new tool for assessing inflammatory potential of diet and associations with cancer

Susan Steck, PhD, MPH, RD
Department of Epidemiology and Biostatistics
Cancer Prevention and Control Program
Affiliated Scholar, Center for Research in Nutrition and Health Disparities
Arnold School of Public Health
University of South Carolina
ssteck@sc.edu

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Chronic inflammation is implicated in cancer and other chronic diseases

Diet can modulate inflammation

- Anti-inflammatory:
  - Phytochemicals and micronutrients found in vegetables and fruit
  - Fiber/Whole grains
  - Certain spices and seasonings
- Pro-inflammatory:
  - Saturated fatty acids
  - Trans fatty acids
  - Cholesterol
- Adherence to healthy diet patterns, such as Mediterranean diet, reduces concentrations of inflammatory biomarkers.

Overall premises

- Inflammatory response is necessary for normal immune response.
- NSAIDs reduce risk of some cancers, but with adverse side effects.
- Dietary modification is likely to be safer, perhaps more beneficial than NSAIDs use.
- Diet as a whole is likely to be more important than single constituents.

Objective was to create a Dietary Inflammatory Index that would:

- Be able to classify an individual's diet ranging from the extremes of pro- to anti-inflammatory and to adapt to diverse populations

- Provide individuals with a tool to modify the inflammatory potential of their diet and researchers with a global measure of this inflammatory potential of the diet

Development of the DII

1) 1943 articles on 45 food parameters identified and scored

2) Weight articles by study design and calculate pro- and anti-inflammation fractions

3) Adjust scores if total weighted articles is <236

4) Inflammatory effect score calculated from 2) and 3)

5) -World composite database for 45 food parameters based on data from 11 countries
-Calculate world mean and standard deviation for each of the 45 food parameters.

Dietary intake made available to the scoring algorithm

6) Based on available dietary intake data calculate z-scores and centered percentiles for each of the food parameters for each individual in the study, based on the world average and standard deviation.

7) Multiply centered percentile by the inflammatory effect score to obtain "component-specific DII score."

8) Sum all of the "component specific DII scores" to create the "overall DII score" for an individual.

Shivappa et al, 2014, PHN

Literature Search Strategy

- **Due to the large number of articles on inflammation, the search was limited to six well known inflammatory markers:**
- IL-1**β**, IL-4, IL-6, IL-10, TNF-**α**, CRP
- A total of 45 food parameters were included in the search
- Variations in the names of food parameters were used to ensure full representation
- Each food parameter was individually combined with the list of inflammatory terms
- A total of 1943 articles published through 2010 qualified and were indexed and scored

Scoring Strategy

One of three possible values was assigned based on the effect of the particular food parameter on each inflammatory biomarker:

+1 if pro-inflammatory

0 if produced no change in inflammatory biomarker

-1 if anti-inflammatory

Articles were weighted by study design

Type of Study	Study Design	Value
Human	Experimental	10
	Prospective Cohort	8
	Case-Control	7
	Cross-sectional	6
Animal	Experimental	5
Cell Culture	Experimental	3

Scoring the 45 food parameters

Using these weighted values, a score for each food parameter was calculated using the following steps:

- *Step 1*: Divide the weighted pro- and anti-inflammatory articles by total weighted number of articles.
- *Step 2*: Subtract the anti-inflammatory fraction from the pro-inflammatory fraction.

Example for Saturated Fat

Effect	Study design	Number of articles	Weighted number of articles	Fraction
Anti-inflammatory	Clinical	0	0	$\frac{9}{205}$ =0.044
	Cohort	0	0	
	Case–control	0	0	
	Cross-sectional	1 × 6 =	6	
	Animal	0	0	
	Cell	1 × 3 =	3	
	Total	**2**	**9**	
Pro-inflammatory	Clinical	3 × 10 =	30	$\frac{97}{205}$ =0.473
	Cohort	0	0	
	Case–control	1 × 7 =	7	
	Cross-sectional	4 × 6 =	24	
	Animal	3 × 5 =	15	
	Cell	7 × 3 =	21	
	Total	**18**	**97**	
No effect	Clinical	3 × 10 =	30	
	Cohort	0	0	
	Case–control	0	0	
	Cross-sectional	9 × 6 =	54	
	Animal	3 × 5 =	15	
	Cell	0	0	
	Total	**15**	**99**	
Overall total		**35**	**205**	

STEP 1

Score = 0·473 – 0·044 = **0·429** STEP 2

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Weighting by the Size of the Literature Base

- The median weighted number of articles for the 45 food parameters was 236
- To adjust for some food parameters having a less robust pool of literature, food parameters with a weighted number of articles less than 236 were adjusted as follows:
  1) Number of weighted articles was divided by 236
  2) The fraction was then multiplied by the score for that food parameter, which resulted in the new adjusted score for each food parameter

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	Cohort	0	0	
	Case–control	0	0	
	Cross-sectional	[illegible]	[illegible]	
	Cell	0	0	
	Total	**15**	**99**	
Overall total		**35**	**205**	

STEP 1

Score = 0·473 – 0·044 = **0·429** STEP 2

0.429 * 205/236 = **0.373** (new adjusted score)

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Food parameters in the DII (truncated list)

Table 2 Food parameters included in the dietary inflammatory index, inflammatory effect scores, and intake values from the global composite data set; Dietary Inflammatory Index Development Study, Columbia, SC, USA, 2011–2012

Food parameter	Weighted number of articles	Raw inflammatory effect score*	Overall inflammatory effect score†	Global daily mean intake‡ (units/d)	SD‡
Alcohol (g)	417	−0·278	−0·278	13·98	3·72
Vitamin B_{12} (μg)	122	0·205	0·106	5·15	2·70
Vitamin B_6 (mg)	227	−0·379	−0·365	1·47	0·74
β-Carotene (μg)	401	−0·584	−0·584	3718	1720
Caffeine (g)	209	−0·124	−0·110	8·05	6·67
Carbohydrate (g)	211	0·109	0·097	272·2	40·0
Cholesterol (mg)	75	0·347	0·110	279·4	51·2
Energy (kcal)	245	0·180	0·180	2056	338
Eugenol (mg)	38	−0·868	−0·140	0·01	0·08
Total fat (g)	443	0·298	0·298	71·4	19·4
Fibre (g)	261	−0·663	−0·663	18·8	4·9
Folic acid (μg)	217	−0·207	−0·190	273·0	70·7
Garlic (g)	277	−0·412	−0·412	4·35	2·90
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MUFA (g)	106	−0·019	−0·009	27·0	6·1
Niacin (mg)	58	−1·000	−0·246	25·90	11·77
n-3 Fatty acids (g)	2588	−0·436	−0·436	1·06	1·06
n-6 Fatty acids (g)	924	−0·159	−0·159	10·80	7·50
Onion (g)	145	−0·490	−0·301	35·9	18·4
Protein (g)	102	0·049	0·021	79·4	13·9
PUFA (g)	4002	−0·337	−0·337	13·88	3·76
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Overall DII score

- More negative scores represent anti-inflammatory diet whereas more positive scores represent pro-inflammatory diet

- Approximate range is -10 to 10

Construct Validation of the DII: Association with inflammatory biomarkers

- Seasonal Variation in Blood Cholesterol Study (SEASONS) (n=~500)
  - DII calculated from 24 hour recalls and structured 7 day food records
  - Third tertile of DII compared to first tertile **associated with 47% to 61% increased odds of having elevated CRP (>3mg/L)**

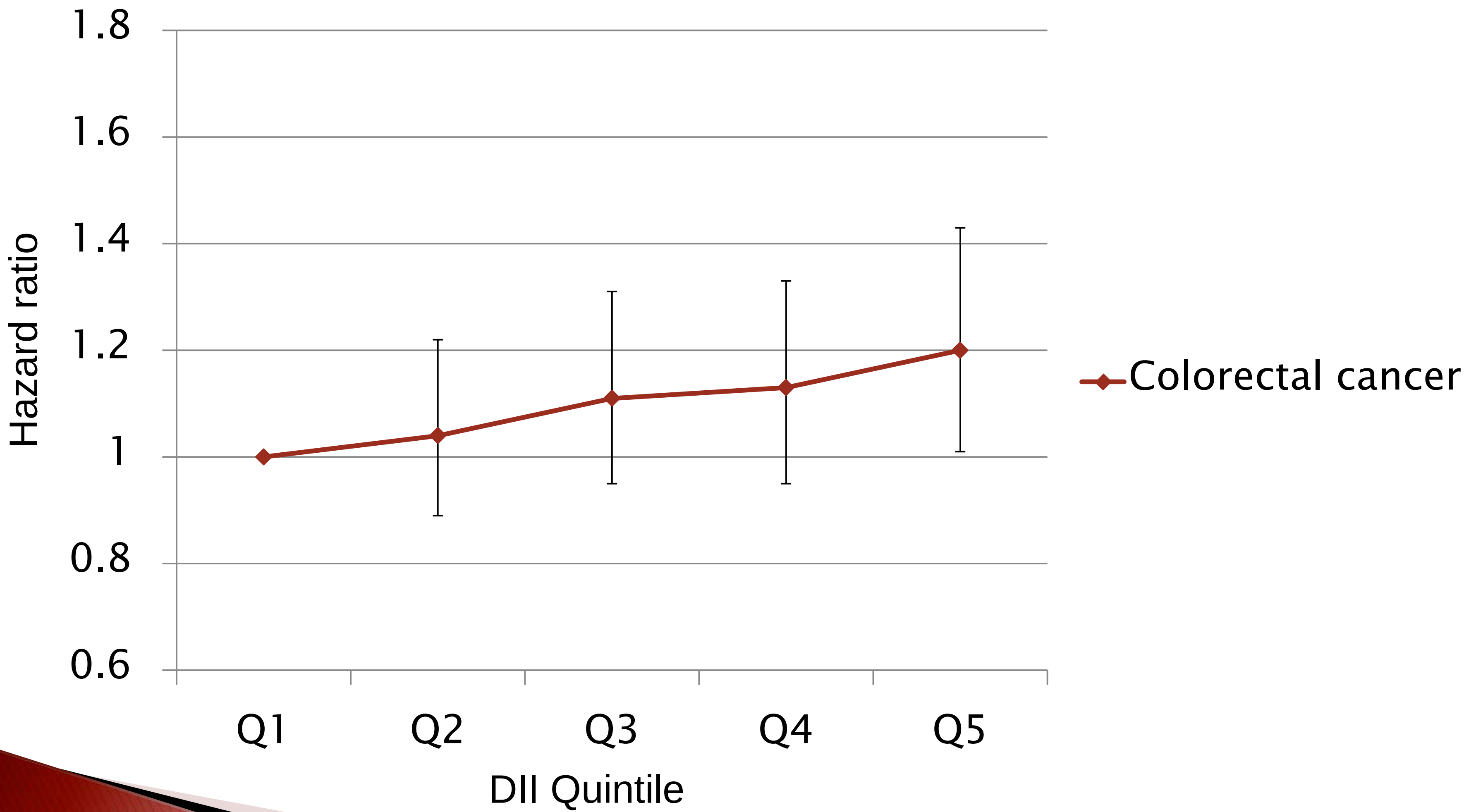
- Women's Health Initiative (WHI) ancillary study (n=2600):
  - DII calculated from baseline FFQ
  - **More pro-inflammatory diet associated with higher:**
    - **IL-6** (p<0.0001)
    - **hs-CRP** [OR for elevated CRP = 1.34 (1.01, 1.78) for Q5 vs Q1]
    - **TNFalpha R2** (p<0.002)
    - **Overall inflammatory biomarker score** derived from a combination of the three biomarkers (p<0.0001)

Associations between the DII and cancer

- Secondary data analyses of prospective cohort studies
  - Iowa Women's Health Study (colorectal cancer)
  - Women's Health Initiative (colorectal and breast cancers)
  - NIH-AARP (colorectal cancers)

- DII calculated from baseline FFQs
- Multiple covariate-adjusted Cox proportional hazards regression models used to calculate hazard ratios (HR) and 95%CIs

Risk of colorectal cancer across quintiles of the DII: Iowa Women's Health Study



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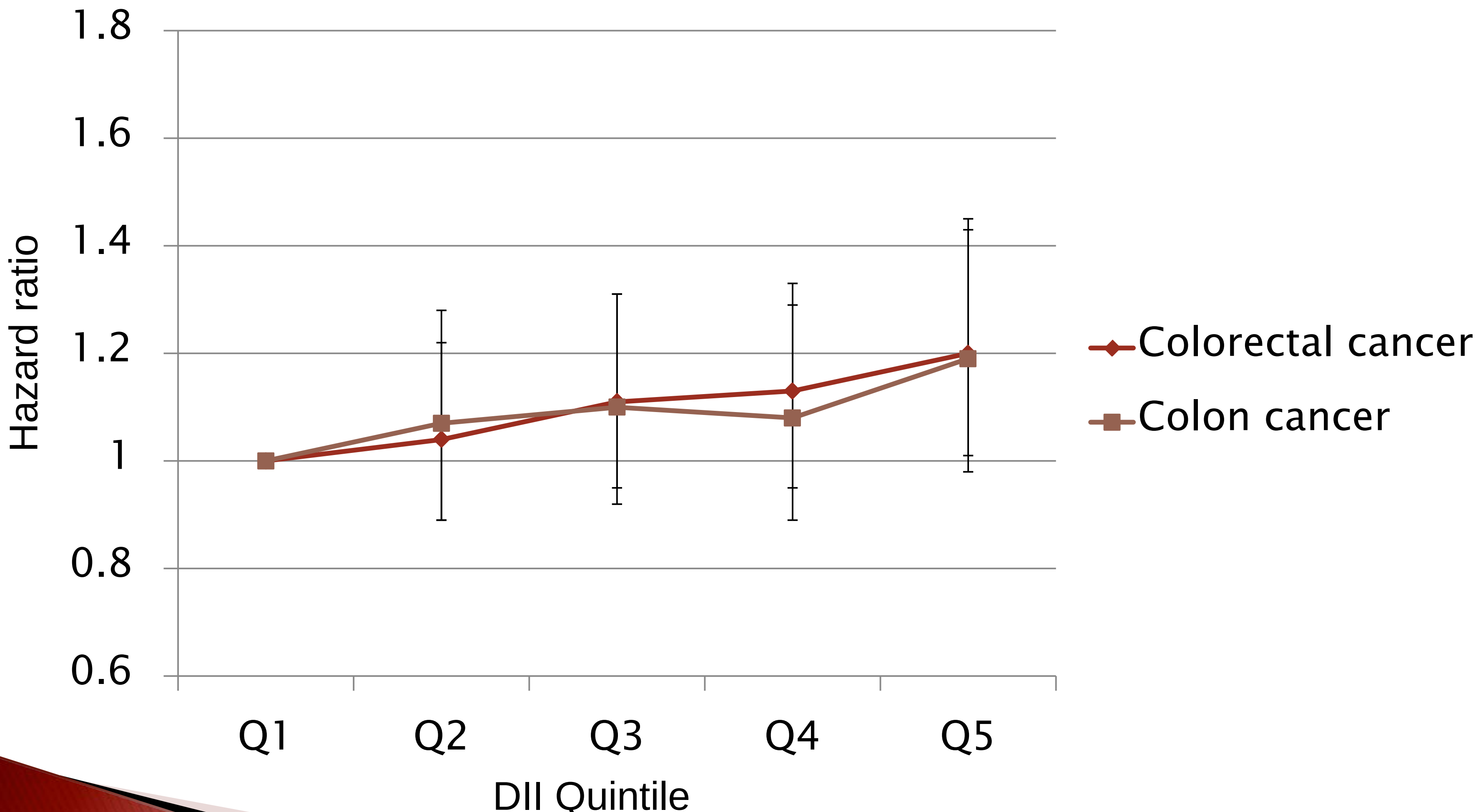

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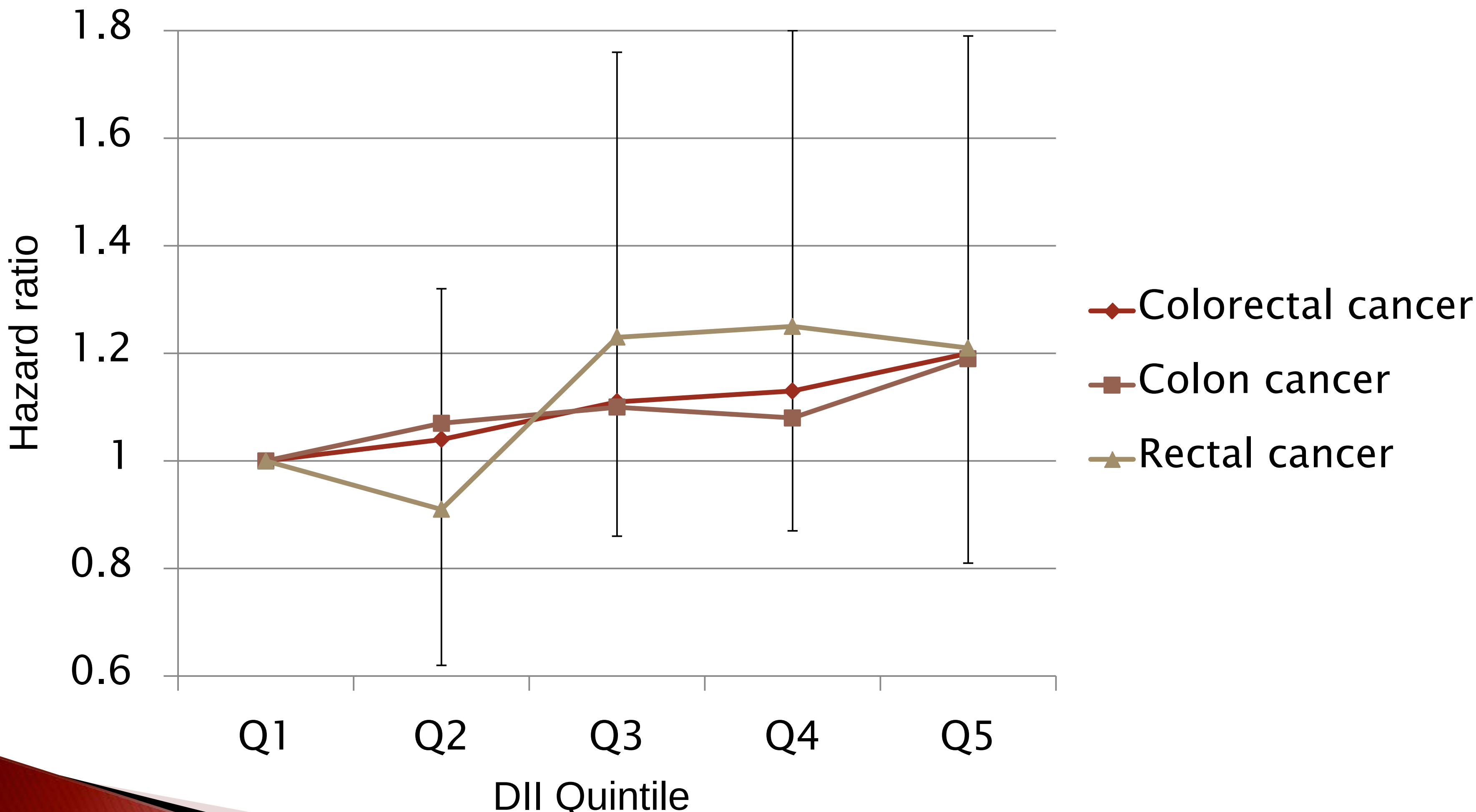

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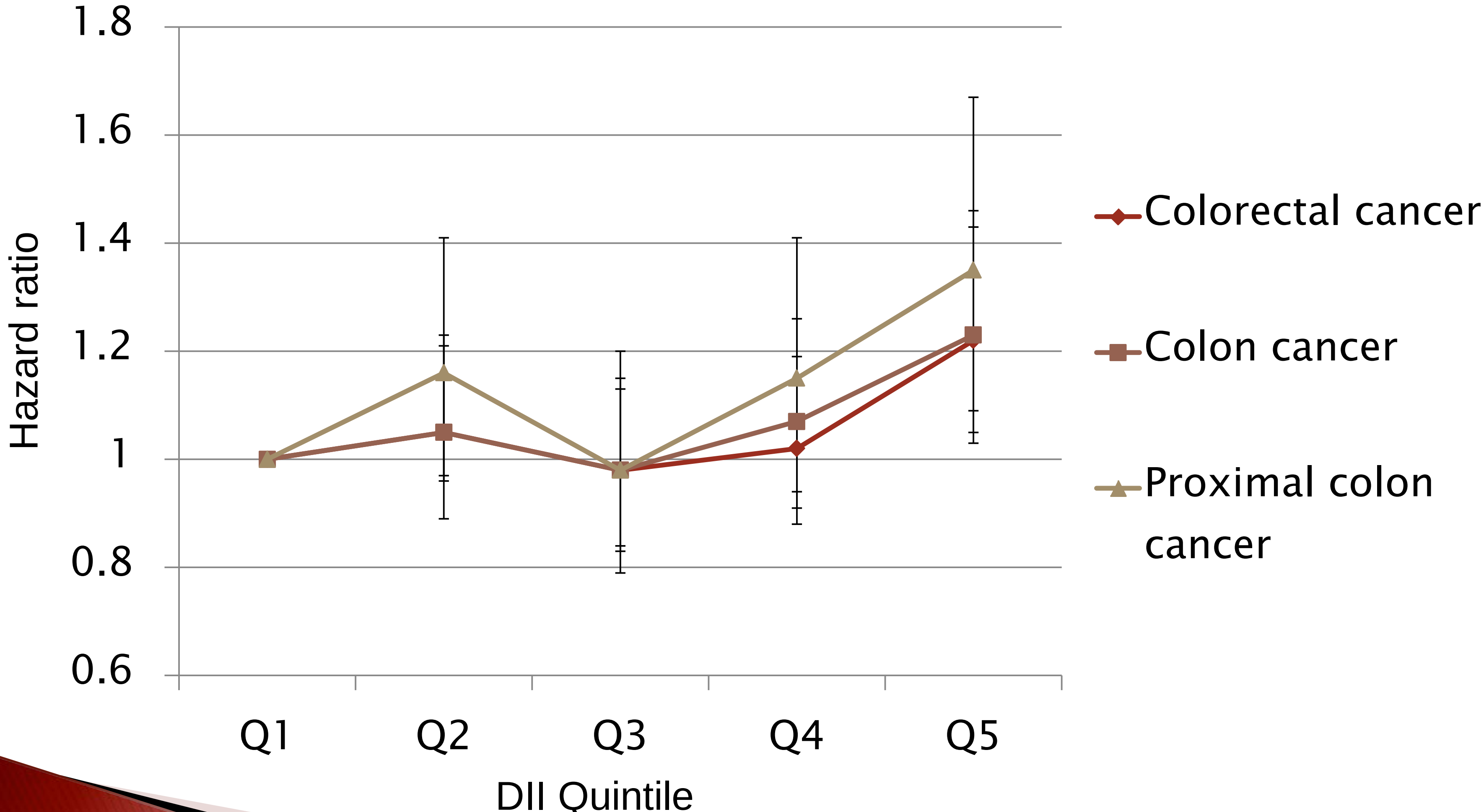
Risk of colorectal cancer across quintiles of the DII: Women's Health Initiative



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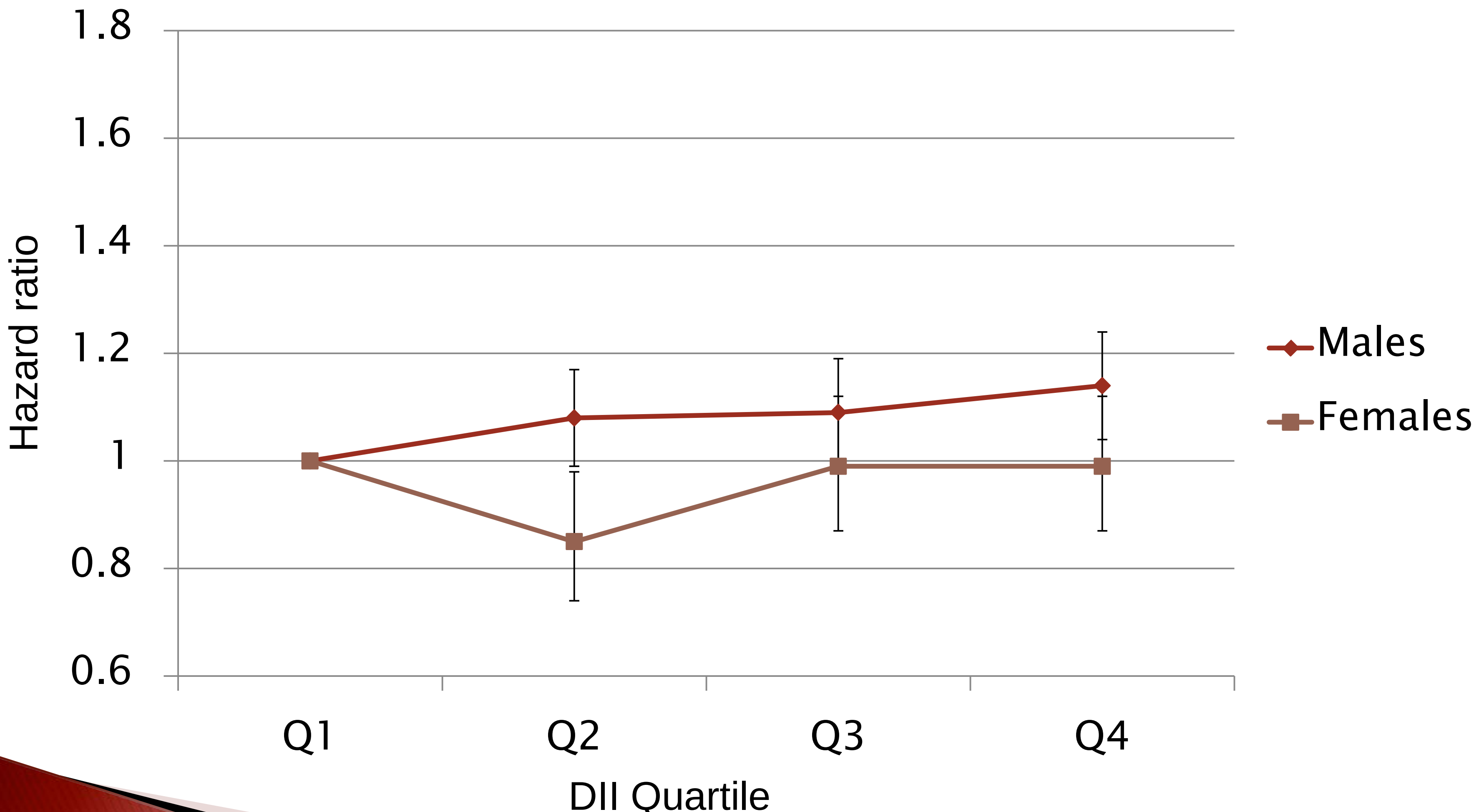
Tabung et al. under review

Risk of colorectal cancer across quartiles of the DII: NIH-AARP Study



Wirth et al. under review

Risk of breast cancer incidence and mortality across DII tertiles: Women's Health Initiative

	T1 (-7.055, <-2.366) (healthiest)	T2 (-2.366, <0.468)	T3 (0.468, 5.789) (least healthy)	P_{trend}
Breast cancer cases, n=5841	2155	1912	1774	
Breast cancer HR (95%CI)[a]	**1.00 (ref)**	**0.95 (0.89, 1.01)**	**0.99 (0.92, 1.06)**	**0.89**
HER2+ cases, n=662	215	222	225	
HER2+ cancer HR (95%CI)[a]	**1.00 (ref)**	**1.12 (0.92, 1.35)**	**1.29 (1.05, 1.59)**	**0.01**
Breast cancer mortality, n=406	117	136	153	
Breast cancer mortality HR (95%CI) [b]	**1.00 (ref)**	**1.06 (0.81, 1.37)**	**1.30 (0.99, 1.71)**	**0.04**

[a]adjusted for age, race/ethnicity, body mass index, physical activity, education, smoking status, mammography within 2 years of baseline, age at menarche, number of live births, oophorectomy status, hormone therapy use, NSAID use, dietary modification trial arm, hormone therapy trial arm, calcium and vitamin D trial arm, and total energy intake; [b]adjusted for age, race/ethnicity, body mass index, physical activity, education, smoking status, mammography within 2 years of baseline, hormone therapy use, NSAID use, dietary modification trial arm, hormone therapy trial arm, calcium and vitamin D trial arm, total energy intake, estrogen receptor status, progesterone receptor status, stage and time since diagnosis

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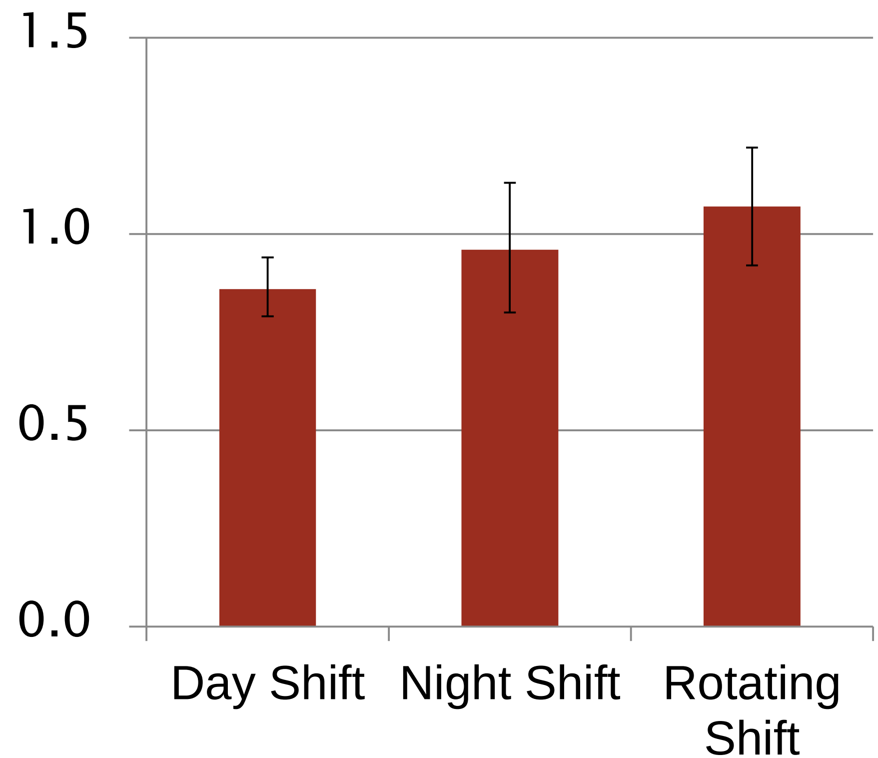
Tabung et al. in preparation

Limitations

- Diet assessment at only one time point (baseline)
- FFQ measurement error
- Generalizability
- Potential residual or unmeasured confounding

Mean DII by Shift Work in NHANES 2005-2010



Wirth et al. 2014 JOEM

Conclusions

- More pro-inflammatory DII scores were associated positively with inflammatory biomarkers.
- More pro-inflammatory DII scores were associated with increased risk of colorectal cancer among postmenopausal women in the IWHS and WHI.
  - Increased risk for men observed in the NIH-AARP though no association for women in NIH-AARP
- The DII was not associated with invasive breast cancer risk
  - Suggestion of increased risk for HER2+ cancers and for breast cancer mortality

Future directions

- Examining DII using post-diagnosis dietary data in relation to cancer survival.
- The DII can be applied in studies utilizing 24 hour recall, food record or FFQ dietary assessment data.
- An "app" is under development to assist clinicians in screening patients, and to help consumers move toward a more anti-inflammatory diet.

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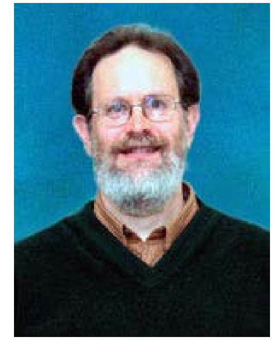

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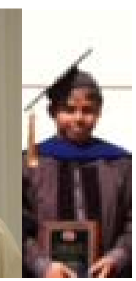

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Acknowledgements: Co-authors

Ilir Agalliu	Albert Einstein College of Medicine
Cindy Blair	University of Minnesota
Bette Caan	Kaiser Permanente Division of Research
Rowan T. Chlebowski	UCLA School of Medicine
Jo L. Freudenheim	SUNY Dept. of Social and Preventive Medicine
Melanie Hingle	Univ. Ariz. Dept. of Nutritional Sciences
Gloria Ho	Albert Einstein College of Medicine
Lifang Hou	Northwestern Univ. Feinberg School of Medicine
David Jacobs	University of Minnesota
Li Jiao	Baylor College of Medicine
Karen K. Johnson	Univ. of Tennessee Health Science Center
Dorothy S. Lane	Stony Brook Univ. School of Medicine
Lisa W. Martin	GWU School of Medicine and Health Sciences
Amy E. Millen	SUNY Dept. of Preventive Medicine
Yasmin Mossavar-Rahmani	Albert Einstein College of Medicine
Hannah L. Park	UC Irvine Dept. of Epidemiology
Anna Prizment	University of Minnesota
Lihong Qi	UC Davis School of Medicine
Milagros C. Rosal	UMass Medical School
James M. Shikany	UAB School of Medicine
Linda Snetselaar	The University of Iowa
Frances A. Tylavsky	Univ. of Tennessee Health Science Center
Mara Z. Vitolins	Wake Forest School of Medicine
Jean Wactawski-Wende	SUNY Dept. of Social and Preventive Medicine

THANK YOU

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Shivappa et al, 2014, PHN

Food parameters in the DII (continued)

Food parameter	Weighted number of articles	Raw inflammatory effect score*	Overall inflammatory effect score†	Global daily mean intake‡ (units/d)	SD‡
Se (μg)	372	−0·191	−0·191	67·0	25·1
Thiamin (mg)	65	−0·354	−0·098	1·70	0·66
Trans fat (g)	125	0·432	0·229	3·15	3·75
Turmeric (mg)	814	−0·785	−0·785	533·6	754·3
Vitamin A (RE)	663	−0·401	−0·401	983·9	518·6
Vitamin C (mg)	733	−0·424	−0·424	118·2	43·46
Vitamin D (μg)	996	−0·446	−0·446	6·26	2·21
Vitamin E (mg)	1495	−0·419	−0·419	8·73	1·49
Zn (mg)	1036	−0·313	−0·313	9·84	2·19
Green/black tea (g)	735	−0·536	−0·536	1·69	1·53
Flavan-3-ol (mg)	521	−0·415	−0·415	95·8	85·9
Flavones (mg)	318	−0·616	−0·616	1·55	0·07
Flavonols (mg)	887	−0·467	−0·467	17·70	6·79
Flavonones (mg)	65	−0·908	−0·250	11·70	3·82
Anthocyanidins (mg)	69	−0·449	−0·131	18·05	21·14
Isoflavones (mg)	484	−0·593	−0·593	1·20	0·20
Pepper (g)	78	−0·397	−0·131	10·00	7·07
Thyme/oregano (mg)	24	−1·000	−0·102	0·33	0·99
Rosemary (mg)	9	−0·333	−0·013	1·00	15·00

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