Can Diet Modulate Inflammation and Reduce Cancer Risk and Improve Survival? Evidence from the WHI

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Diet and Chronic Inflammation

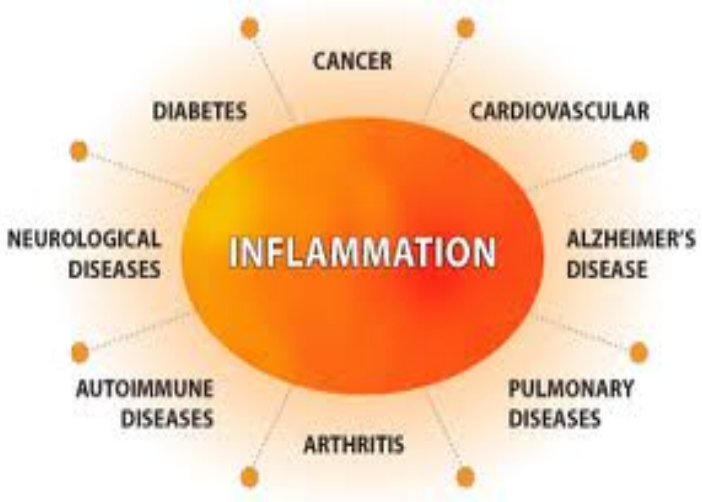
Anti-inflammatory:

- Phytochemicals and micronutrients found in vegetables and fruits
- Fiber/Whole grains
- Certain spices and seasonings

Pro-inflammatory:

- Saturated fatty acids
- Trans fatty acids
- Cholesterol

Diet as a whole is likely to be more important than single constituents.



The Dietary Inflammatory Index (DII)

DII is a literature-derived, population-based index of overall diet quality with regards to its inflammatory potential.

DII assesses an individual's diet on a continuum from maximally anti-inflammatory to maximally pro-inflammatory.

Development of the DII: Literature Search Strategy

- Due to the large number of articles on inflammation, the search was limited to six well known inflammatory markers:

IL-1β, IL-4, IL-6, IL-10, TNF-α, CRP

- A total of 45 dietary factors were identified in the search
- Variations in the names of dietary factors were used to ensure full representation
- Each dietary factor was individually combined with the list of inflammation terms
- A total of 1943 articles published through 2010 were scored

Development of the DII: Scoring Strategy

One of three possible values was assigned based on the effect of the particular dietary factor 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

Development of the DII: Scoring the 45 dietary factors

A score for dietary factor was calculated as follows:

- 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.

Scores were adjusted by size of the literature base:

- The median weighted number of articles for all of the dietary factors was 236
- To adjust for some dietary factors having a less robust pool of literature, factors with a weighted number of articles <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 factor, which resulted in the new adjusted score for the dietary factor

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**	STEP 1
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	
	Animal	3 × 5 =	15	
	Cell	0	0	
	Total	**15**	**99**	
Overall total		**35**	**205**	
Score = 0·473 – 0·044 = **0·429**				STEP 2

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

Shivappa et al, 2014 PHN

Summary of Steps in Calculating the DII

1) 1943 articles on 45 dietary factors 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) -Global composite database for 45 dietary factors based on data from 11 countries
-Calculate global mean and standard deviation for each of the 45 dietary factors.

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 dietary factor for each individual in the study, based on the global 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

The 45 DII Components and Corresponding Inflammatory Effect Scores

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
Ginger (g)	182	−0·588	−0·453	59·0	63·2
Fe (mg)	619	0·032	0·032	13·35	3·71
Mg (mg)	351	−0·484	−0·484	310·1	139·4
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
Riboflavin (mg)	22	−0·727	−0·068	1·70	0·79
Saffron (g)	33	−1·000	−0·140	0·37	1·78
Saturated fat (g)	205	0·429	0·373	28·6	8·0

Shivappa et al, 2014, PHN

The 45 DII Components and Corresponding Inflammatory Effect Scores (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

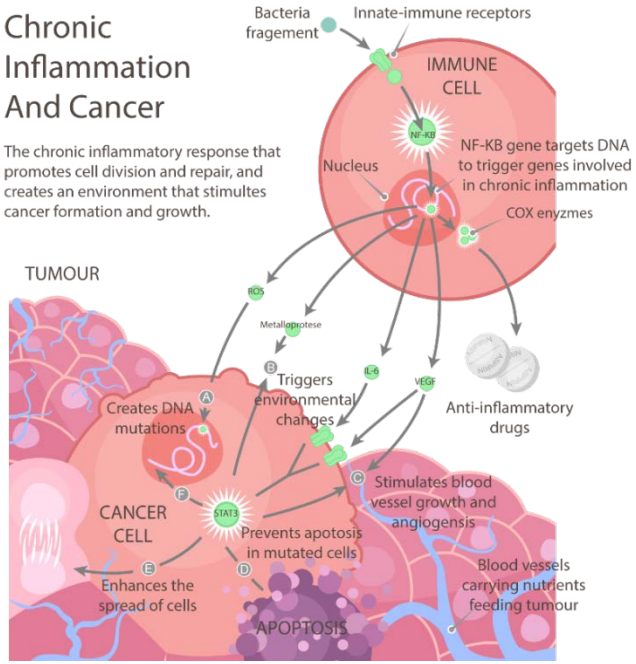
Shivappa et al, 2014, PHN

Overall DII Score

- More negative scores represent anti-inflammatory diet whereas more positive scores represent pro-inflammatory diet
- DII in the WHI FFQ: calculated using 32 out of the 45 original DII components

-10 ⟷ +10

Approximate range



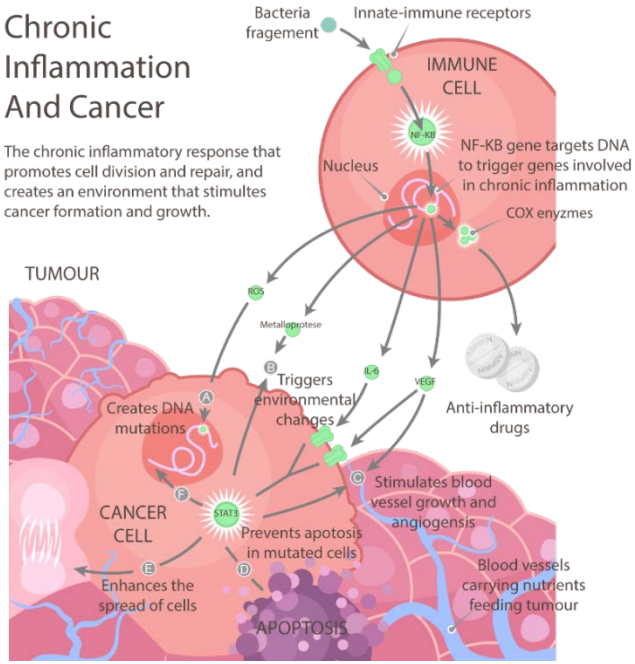
Construct Validation of the DII: Associations with Inflammatory Markers

Table 1. Association Between Quintiles of the FFQ-derived DII and Biomarkers of Inflammation, WHI Ancillary Study

Inflammatory biomarker	Q1	Q3	Q5	P_{trend}
IL-6	referent	-0.002 (-0.03, 0.02)	**0.05 (0.03, 0.08)**	<0.0001
hs-CRP (continuous)	referent	-0.01 (-0.04, 0.03)	0.002 (-0.03, 0.03)	0.20
hs-CRP (dichotomous)	referent	1.28 (0.97, 1.69)	**1.34 (1.01, 1.78)**	0.22
TNFα-R2	referent	-11.77 (-71.68, 48.14)	**82.75 (20.84, 144.66)**	0.002
Overall inflammatory biomarker	referent	0.11 (-0.02, 0.24)	**0.27 (0.14, 0.41)**	<0.0001

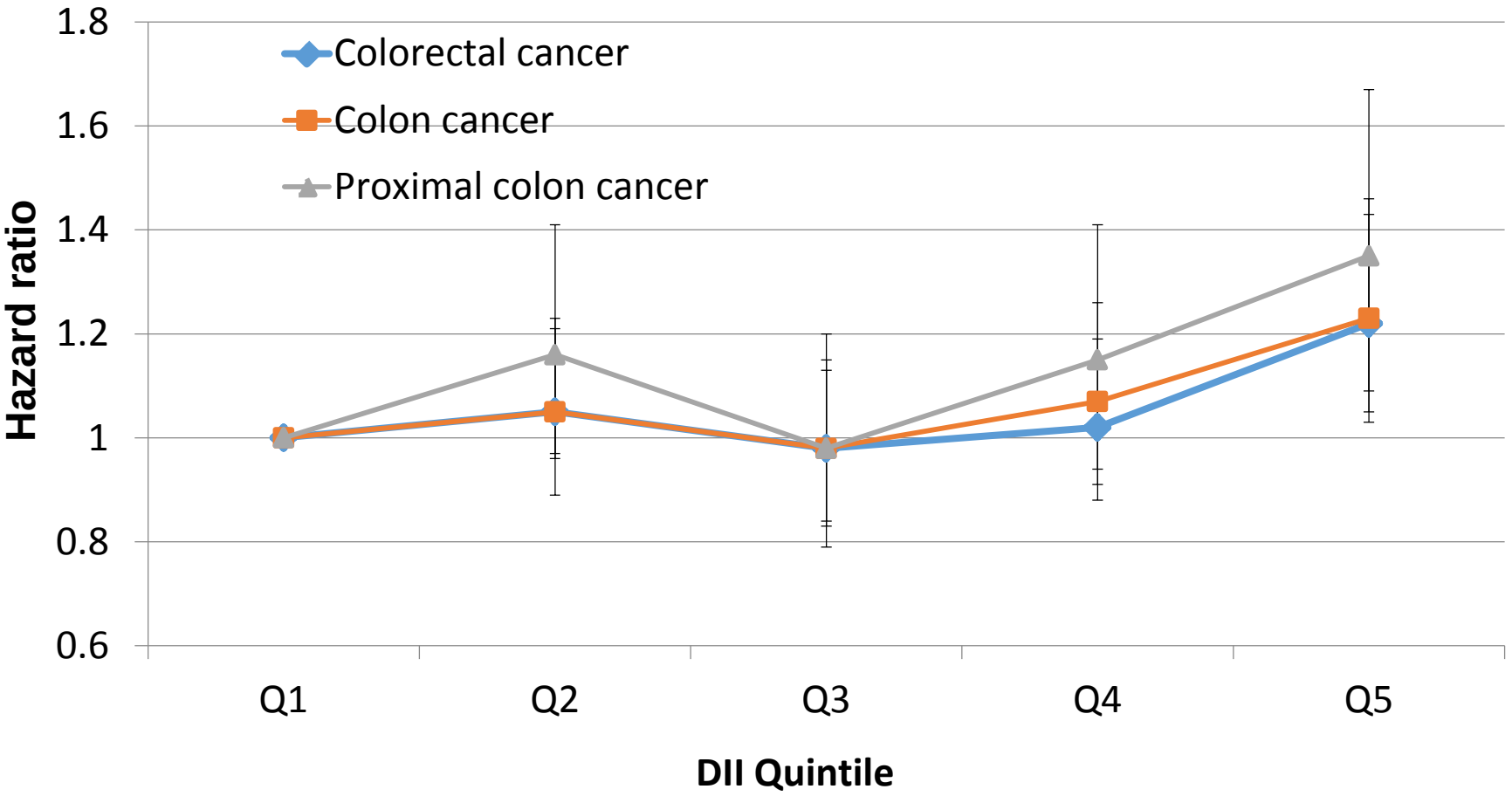
- **Values are mean biomarker concentrations (back transformed for IL6 and CRP)**
- **n=~2600**
- **Models adjusted for age, body mas index, race/ethnicity, educational level, smoking status, physical activity, use of NSAIDs, statins, inflammation-related co-morbidities (history of ulcerative colitis, diabetes, Alzheimer's disease, arthritis, hypertension, cancer, and hypercholesterolemia)**

Tabung et al. 2015, Annals of Epidemiology



Associations Between the DII and Colorectal and Breast Cancers: Baseline DII

Fig. 1: Risk of Colorectal Cancer Across DII Quintiles



No significant association for rectal cancer
Multivariable Cox models adjusted for: age, total energy intake, body mass index, race/ethnicity, physical activity, educational level, smoking status, family history of colorectal cancer, hypertension, diabetes, arthritis, history of colonoscopy, history of occult blood tests, NSAID use, category and duration of estrogen use, category and duration of estrogen and progesterone use, dietary modification trial arm, hormone therapy trial arm, and calcium and vitamin D arm

Tabung et al. 2015 Cancer Causes and Control

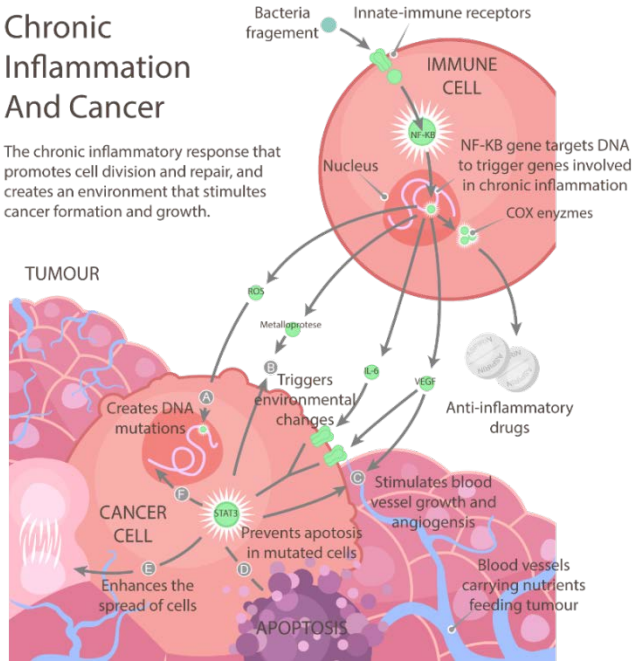
Table 2: Risk of Breast Cancer Incidence and Death Across DII Quintiles

	Q1 (-7.06, <-3.16) (most anti-inflammatory)	Q3 (-2.02, < -0.36)	Q5 (1.90, 5.52) (most pro-inflammatory)	P_{trend}
Breast cancer cases, n=7495	1601	1429	1405	
HR (95%CI)[a]	**1.00 (ref)**	**0.93 (0.86, 1.00)**	**0.99 (0.91, 1.07)**	**0.83**
HER2+ cases, n=771	139	163	140	
HR (95%CI)[a]	**1.00 (ref)**	**1.21 (0.96, 1.52)**	**1.11 (0.85, 1.44)**	**0.24**
Breast cancer death, n=667	108	138	142	
HR (95%CI)[b]	**1.00 (ref)**	**1.25 (0.97, 1.62)**	**1.33 (1.01, 1.76)**	**0.03**

[a]Cox models adjusted for age, race/ethnicity, BMI, 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

Tabung et al., 2016, British Journal of Cancer

Changes in DII Over Time



Mean DII scores computed at different time points and used to describe changes over time in the DII:

OS: Baseline and Year 3

DM: Year 1, composite Years 3 (Years 2, 3 and 4) and composite Year 6 (Years 5, 6 and 7)

Fig. 2: Mean DII Scores Across Years of Follow-up by Study arm

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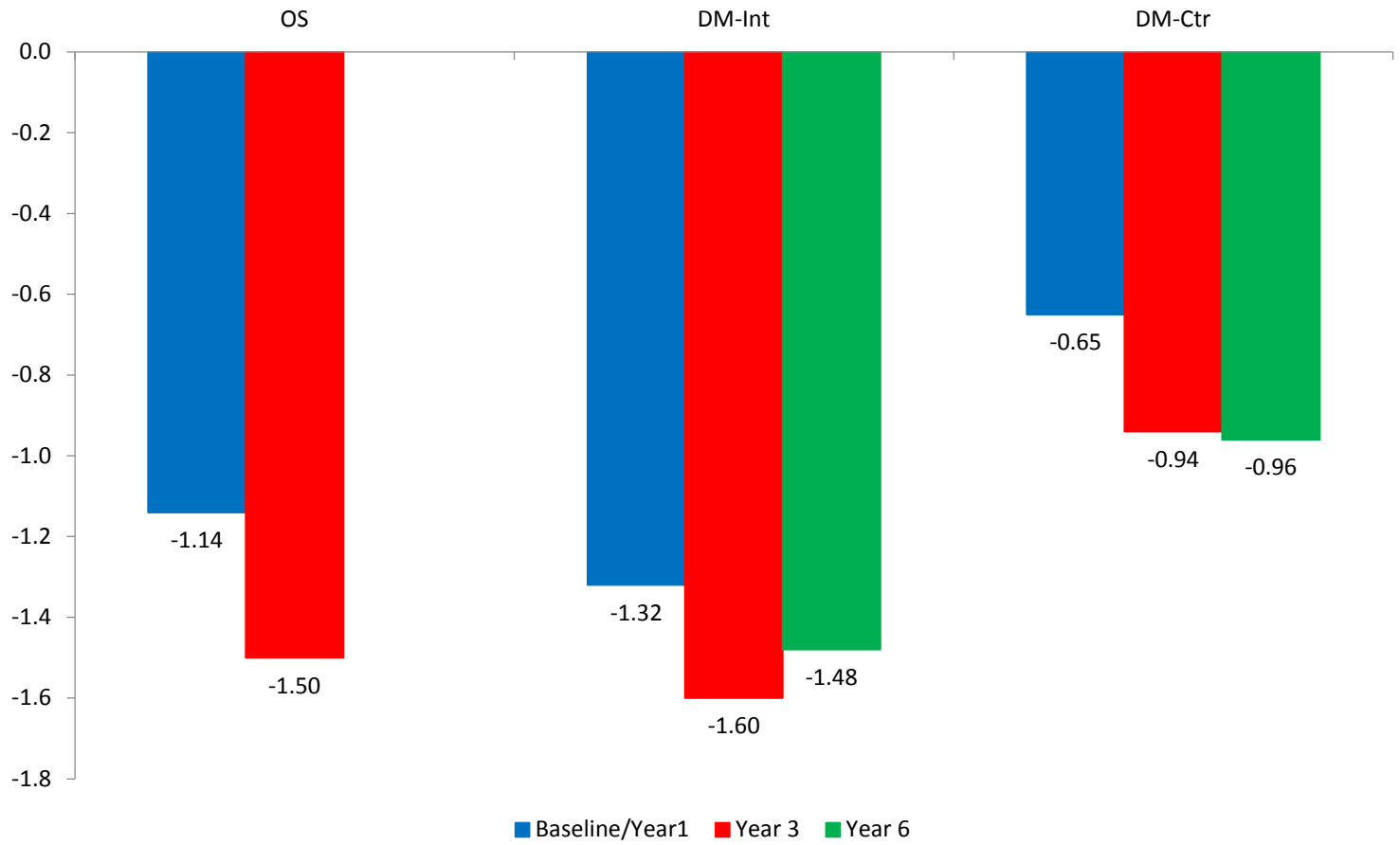


OS=Observational Study
DM-Int=DM intervention group
DM-Ctr=DM control group

Fig. 3: Mean DII Over Time by BMI Status and DM arm

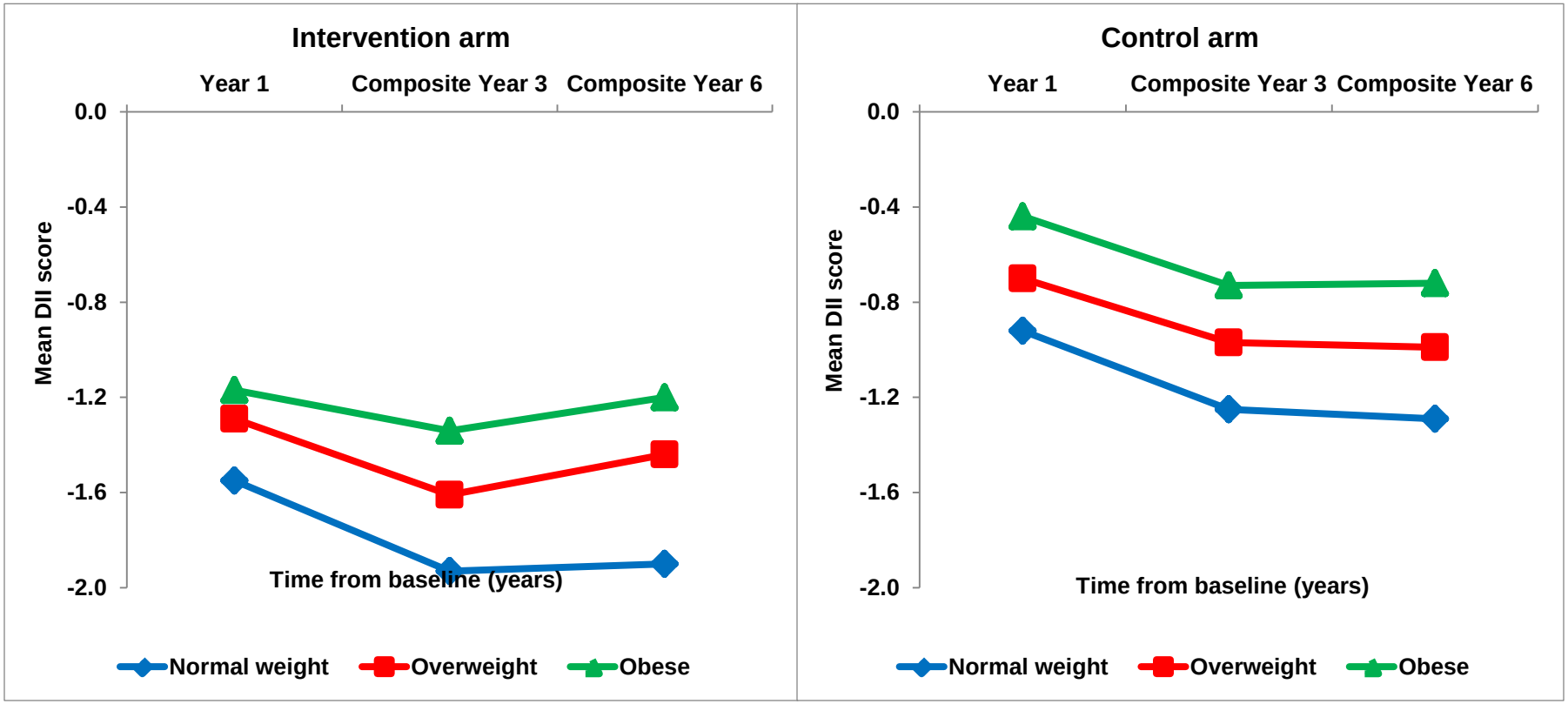
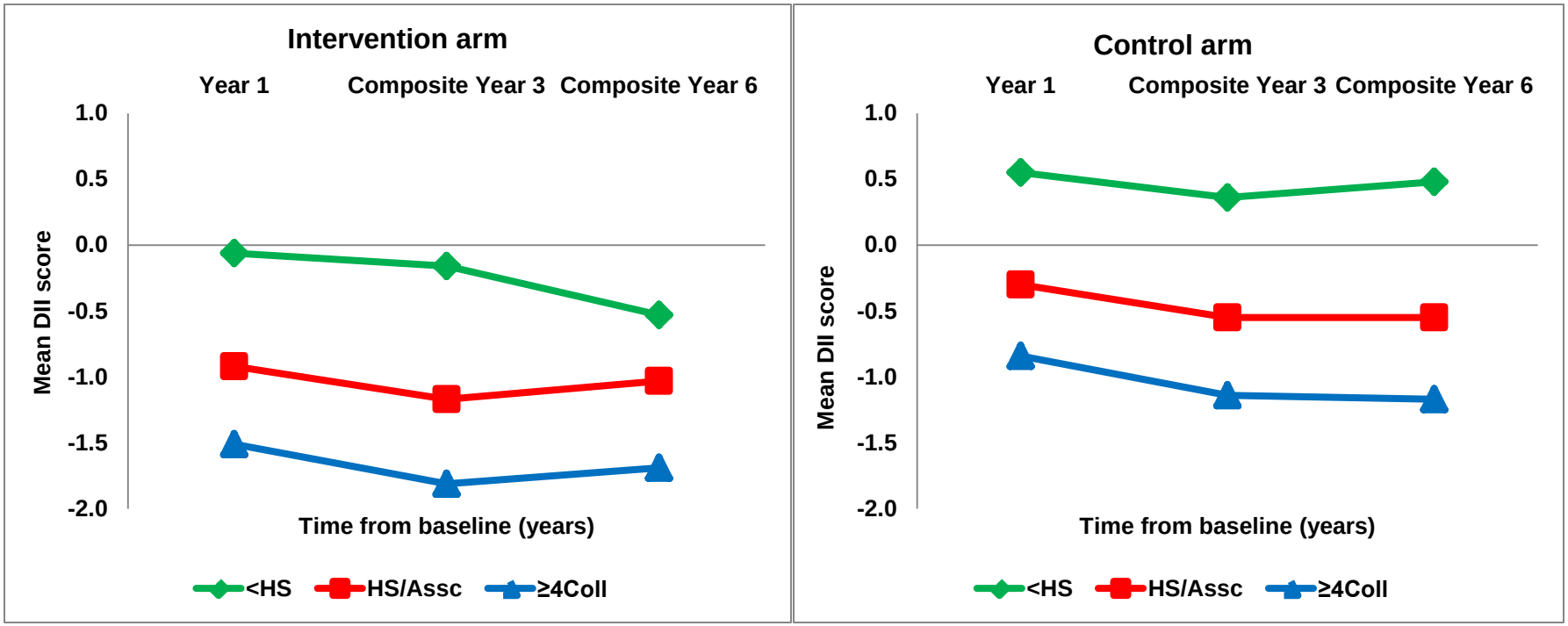
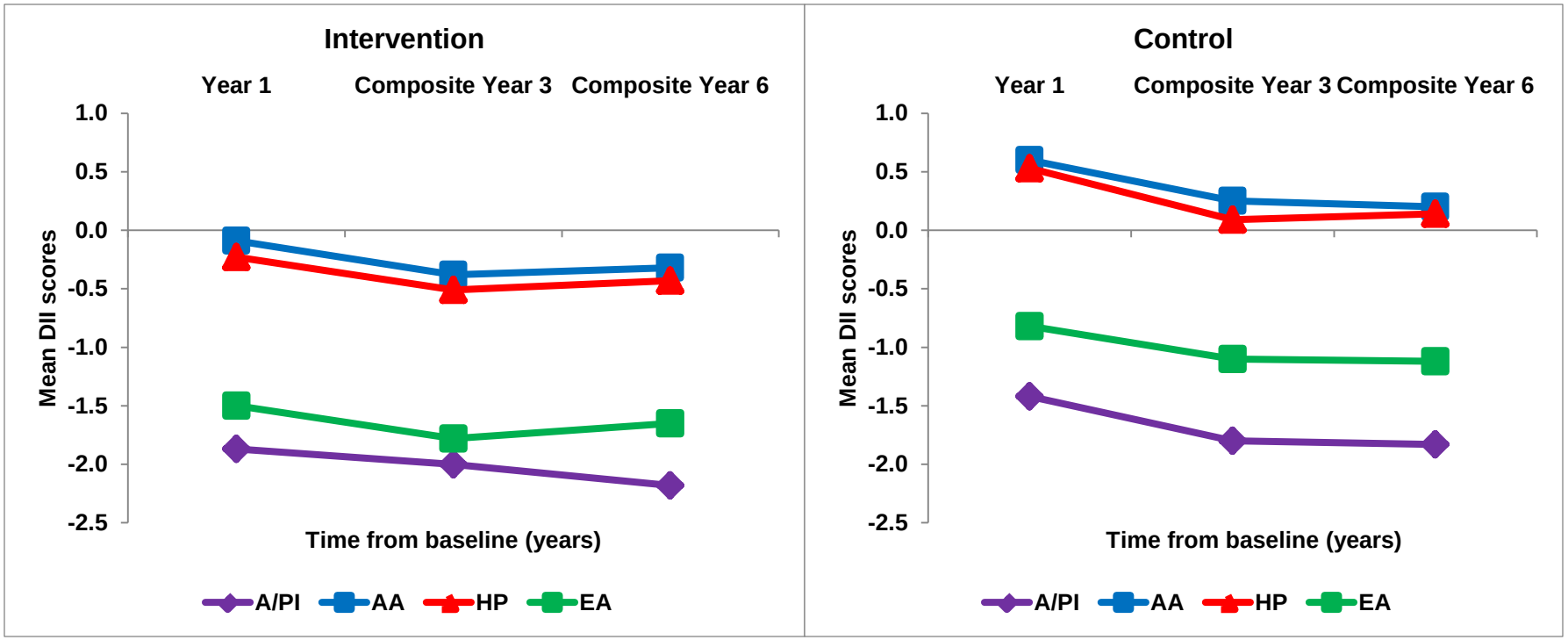


Fig. 4: Mean DII Scores Over Time by Educational Level and DM arm



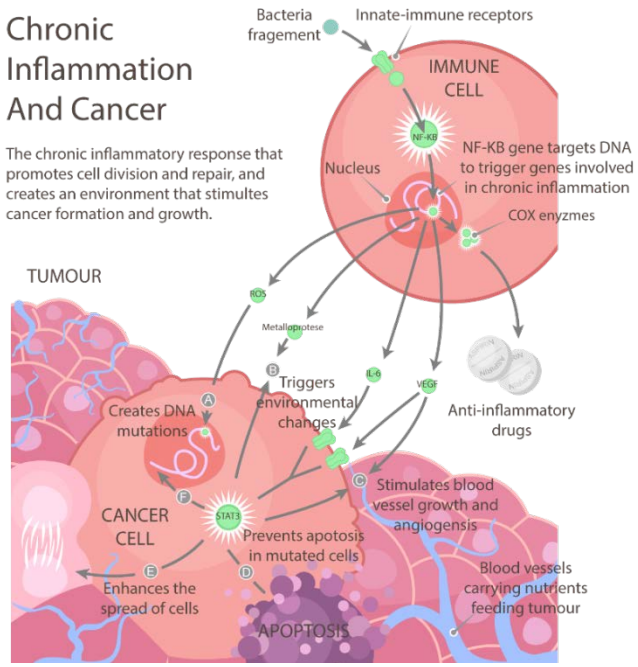
- <HS= High school graduate
- HS/Assc= High school graduate/some college or associate degree
- ≥4Coll = ≥4 years of college

Fig. 5: Mean DII Scores Over Time by Race/Ethnicity and DM arm



- A/PI=Asian/Pacific Islander
- AA=African American
- HP=Hispanic
- EA=European American

Associations Between Changes in DII and Colorectal and Breast Cancers



Assessed using a 5-level variable constructed based on changes in DII quintiles at two time points: baseline and Year 3

Cumulative average DII also calculated between baseline and Year 3

Both exposure variables used to assess risk of colorectal cancer and breast cancers

Participants: OS and DM control group

Changes in DII Over Time

- **Anti-inflammatory stable**: Q1 or Q2 at both time points or change from Q3 to Q2;
- **Anti-inflammatory change**: changes ≤ -2Q;
- **Neutral inflammation stable**: changes from Q2 to Q3, Q4 to Q3 or stable at Q3 at both time points;
- **Pro-inflammatory change**: changes ≥ 2Q;
- **Pro-inflammatory stable**: Q4 or Q5 at either time points, or change from Q3 to Q4.

Cumulative Average DII

- OS: baseline and Year 3
- DM control arm: Year 1 and composite Year 3 (years 2, 3 and 4)
  - FFQs at Years 7 and beyond, not used because of smaller sample sizes

Table 3: Patterns of Change in DII and Colorectal Cancer Risk

	Anti-inflammatory stable (Referent)	Anti-inflammatory change	Neutral inflammation stable	Pro-inflammatory change	Pro-inflammatory stable
All participants					
Colorectal cancer, n=976	1.00	1.10 (0.89, 1.36)	0.97 (0.80, 1.17)	1.15 (0.92, 1.43)	1.10 (0.92, 1.32)
Colon cancer, n=802	1.00	1.13 (0.89, 1.43)	1.02 (0.83, 1.26)	1.13 (0.88, 1.46)	1.14 (0.94, 1.39)
Rectal cancer, n=174	1.00	0.98 (0.59, 1.63)	0.75 (0.47, 1.20)	1.23 (0.75, 2.02)	0.93 (0.61, 1.42)
Non users of non-steroidal anti-inflammatory drugs					
Colorectal cancer, n=419	1.00	1.06 (0.76, 1.50)	0.86 (0.62, 1.18)	1.20 (0.85, 1.71)	**1.42 (1.08, 1.85)**
Colon cancer, n=348	1.00	1.05 (0.72, 1.53)	0.93 (0.63, 1.27)	1.16 (0.79, 1.70)	**1.40 (1.05, 1.88)**
Rectal cancer, n=71	1.00	1.15 (0.51, 2.62)	0.65 (0.28, 1.64)	1.49 (0.66, 3.35)	1.47 (0.76, 2.84)
Regular users of non-steroidal anti-inflammatory drugs					
Colorectal cancer, n=557	1.00	1.13 (0.86, 1.50)	1.04 (0.82, 1.32)	1.11 (0.83, 1.48)	0.89 (0.70, 1.13)
Colon cancer, n=454	1.00	1.19 (0.88, 1.63)	1.10 (0.85, 1.44)	1.10 (0.80 1.53)	0.95 (0.73, 1.24)
Rectal cancer, n=103	1.00	0.91 (0.48, 1.72)	0.81 (0.46, 1.41)	1.10 (0.58, 2.08)	0.65 (0.36, 1.13)

Models were adjusted for age, race/ethnicity, educational level, smoking status, diabetes, hypertension, arthritis, regular NSAID use (except when stratified by NSAIDs use), category and duration of estrogen use, category and duration of estrogen & progesterone use, body mass index, physical activity and total energy intake

Table 4: Cumulative Average DII and Colorectal Cancer Risk

	Quintile 1 (more anti-inflammatory diet) referent	Quintile 2	Quintile 3	Quintile 4	Quintile 5 (more pro-inflammatory diet)	P_{trend}
All participants						
Colorectal cancer, n=976	1.00	1.08 (0.88, 1.32)	1.12 (0.92, 1.38)	0.88 (0.71, 1.10)	**1.29 (1.04, 1.60)**	**0.11**
Colon cancer, n=802	1.00	1.12 (0.90, 1.41)	1.17 (0.93, 1.47)	0.92 (0.72, 1.17)	**1.38 (1.09, 1.74)**	**0.05**
Rectal cancer, n=174	1.00	0.90 (0.57, 1.43)	0.94 (0.59, 1.50)	0.76 (0.46, 1.25)	0.98 (0.60, 1.61)	0.82
Non users of non-steroidal anti-inflammatory drugs						
Colorectal cancer, n=419	1.00	1.16 (0.84, 1.60)	1.30 (0.94, 1.79)	0.96 (0.68, 1.35)	**1.64 (1.19, 2.27)**	**0.01**
Colon cancer, n=348	1.00	1.12 (0.78, 1.61)	1.28 (0.90, 1.81)	0.99 (0.68, 1.43)	**1.67 (1.17, 2.38)**	**0.01**
Rectal cancer, n=71	1.00	1.36 (0.62, 2.98)	1.43 (0.65, 3.13)	0.85 (0.35, 2.04)	1.61 (0.72, 3.61)	0.51
Regular users of non-steroidal anti-inflammatory drugs						
Colorectal cancer, n=557	1.00	1.03 (0.79, 1.33)	1.02 (0.78, 1.33)	0.85 (0.64, 1.12)	1.07 (0.81, 1.43)	0.98
Colon cancer, n=454	1.00	1.12 (0.84, 1.49)	1.10 (0.82, 1.48)	0.88 (0.64, 1.21)	1.18 (0.86, 1.63)	0.72
Rectal cancer, n=110	1.00	0.71 (0.40, 1.28)	0.74 (0.41, 1.34)	0.73 (0.40, 1.34)	0.70 (0.36, 1.36)	0.38

Table 5: Patterns of Change in DII and Breast Cancer Risk

	Anti-inflammatory stable	Anti-inflammatory change	Neutral inflammation stable	Pro-inflammatory change	Pro-inflammatory stable
Invasive breast cancer	1.00	0.93 (0.83, 1.05)	0.95 (0.86, 1.05)	1.01 (0.89, 1.15)	1.06 (0.95, 1.18)
Triple negative (ER−, PR−, HER2−)	1.00	1.30 (0.89, 1.98)	0.98 (0.68, 1.42)	1.23 (0.77, 1.97)	1.40 (0.96, 2.04)
(ER−, PR−, HER2+)	1.00	1.80 (0.91, 3.54)	1.07 (0.55, 2.05)	1.01 (0.42, 2.43)	**1.84 (0.96, 3.54)**
Luminal A (ER+ and/or PR+, HER2−)	1.00	0.88 (0.75, 1.02)	0.92 (0.82, 1.04)	1.03 (0.88, 1.21)	0.97 (0.85, 1.11)
Luminal B (ER+ and/or PR+, HER2+)	1.00	0.70 (0.43, 1.12)	1.00 (0.70, 1.41)	0.89 (0.54, 1.48)	1.18 (0.80, 1.73)
Ductal carcinoma	1.00	0.91 (0.78, 1.06)	0.91 (0.80, 1.03)	0.99 (0.84, 1.18)	1.05 (0.91, 1.20)
Lobular carcinoma	1.00	1.25 (0.87, 1.81)	1.13 (0.82, 1.54)	1.22 (0.80, 1.85)	1.21 (0.86, 1.71)

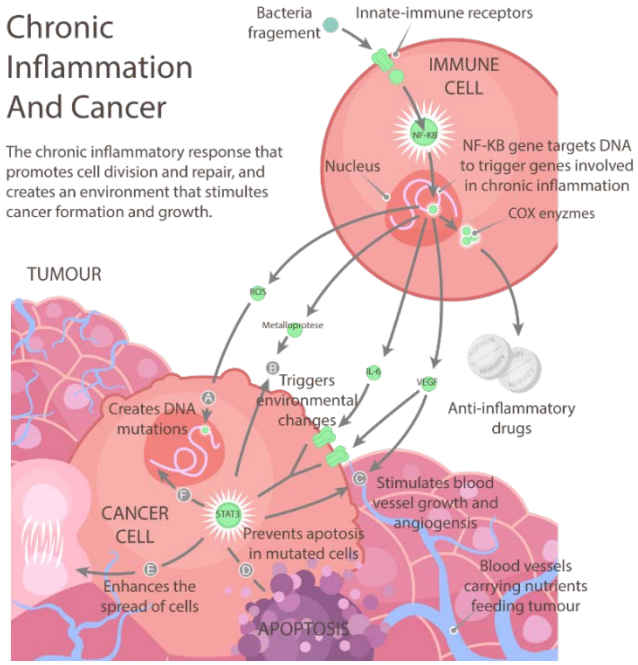
All models were adjusted for age, race/ethnicity, educational level, smoking status, body mass index, physical activity, regular NSAID use, category and duration of estrogen and progesterone use, family history of breast cancer, mammography use within 2 years of baseline, age at menarche, number of live births, oophorectomy status, hormone therapy use, HRT arm, CaD arm and total energy intake

Table 6: Cumulative Average DII and Breast Cancer Risk

	Quintile 1 (more anti-inflammatory diet)	Quintile 2	Quintile 3	Quintile 4	Quintile 5 (more pro-inflammatory diet)	
Invasive breast cancer	1.00	0.98 (0.88, 1.08)	0.97 (0.87, 1.08)	0.90 (0.80, 1.01)	1.02 (0.90, 1.16)	0.71
Triple negative (ER−, PR−, HER2−)	1.00	1.38 (0.95, 1.99)	0.88 (0.57, 1.34)	1.21 (0.79, 1.84)	1.41 (0.90, 2.21)	0.31
(ER−, PR−, HER2+)	1.00	1.94 (0.98, 3.84)	1.51 (0.72, 3.18)	1.04 (0.45, 2.38)	**2.34 (1.06, 5.14)**	**0.18**
Luminal A (ER+ and/or PR+, HER2−)	1.00	0.92 (0.81, 1.05)	0.96 (0.84, 1.09)	0.83 (0.72, 0.97)	0.92 (0.79, 1.08)	0.13
Luminal B (ER+ and/or PR+, HER2+)	1.00	0.93 (0.64, 1.35)	0.83 (0.55, 1.24)	0.86 (0.56, 1.32)	1.06 (0.67, 1.67)	0.90
Ductal carcinoma	1.00	0.97 (0.85, 1.11)	0.92 (0.80, 1.06)	0.92 (0.79, 1.07)	1.02 (0.87, 1.20)	0.83
Lobular carcinoma	1.00	1.14 (0.81, 1.61	1.19 (0.83, 1.69)	1.10 (0.75, 1.61)	1.24 (0.82, 1.87)	0.39

All models were adjusted for age, race/ethnicity, educational level, smoking status, body mass index, physical activity, regular NSAID use, category and duration of estrogen and progesterone use, family history of breast cancer, mammography use within 2 years of baseline, age at menarche, number of live births, oophorectomy status, hormone therapy use, HRT arm, CaD arm and total energy intake

Post-diagnosis DII and Cancer Survival



Utilized FFQs collected after cancer diagnosis.

Examined associations between post-diagnosis DII and all-cause mortality.

Analyses included 4,218 women with a cancer diagnosis (representing 19.2% of total cancer cases in WHI) and 1,459 deaths from any cause

Table 7: Association of Post-Cancer Diagnosis DII Scores and Risk of All-Cause Mortality

	Most anti-inflammatory diet Quartile 1	Quartile 2	Quartile 3	Most pro-inflammatory diet Quartile 4	Ptrend
DII score range	(-7.001, -4.409)	(-4.408, -3.358)	(-3.357, -1.848)	(-1.847, 3.790)	
Sample size(n)	1054	1055	1054	1055	
All-cause deaths (n)	294	346	379	440	
Age-adjusted HR (95%CI)	1.00 (ref)	1.23 (1.06-1.44)	1.45 (1.25-1.69)	1.89 (1.63-2.20)	<.0001
Multivariable-adjusted HR (95%CI)	1.00 (ref)	1.23 (1.05-1.44)	1.38 (1.18-1.62)	1.75 (1.49-2.05)	<.0001

Cox models adjusted for age at baseline (continuous), total energy intake, WHI component (OS, DM-intervention, DM-control), race/ethnicity, education, cancer stage (localized, regional, distant, unknown), BMI, years from cancer diagnosis to FFQ (continuous), physical activity in MET-h/week, current smoking (yes, no, missing)

Zheng et al., 2016 (abstract presented at 2016 ASPO meeting and published in CEBP)

Conclusions

- Pro-inflammatory diets are positively associated with inflammatory markers.
- Pro-inflammatory diets are associated with higher risk of colorectal cancer, especially proximal colon cancer.
- NSAIDs use may modify the association between dietary inflammatory potential and colorectal cancer, with higher risk observed for pro-inflammatory diets among non-regular users of NSAIDs.

Conclusions (continued)

- There may not be a substantial association between dietary inflammatory potential and overall invasive breast cancer risk, though risk of (ER−, PR−, HER2+) breast cancers may be nonlinearly increased.

- More pro-inflammatory diets at baseline were associated with increased risk of breast cancer death.

- Diet ***after*** diagnosis is associated with all-cause mortality; more pro-inflammatory diets were associated with increased risk of all-cause mortality among women diagnosed with cancer.

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