Title Page

Title: Pre-Diagnosis Dietary Patterns and Risk of Multiple Myeloma in the NIH-AARP Diet and Health Study

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Competing Interests

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Keywords

Multiple Myeloma, Diet, Dietary Pattern, Nutrition, Plasma cell disorders

Abstract

Background: Despite patient interest in knowing whether diet is linked to multiple myeloma (MM), there is limited research on dietary patterns and MM risk. Two studies have assessed this risk, albeit with a small number of MM cases. The EPIC-Oxford cohort and Oxford Vegetarian study (65 MM cases) showed that fish eaters, vegetarians and vegans had significantly reduced MM risk compared to meat eaters. The Nurses' Health Study and Health Professionals Follow-up Study (478 MM cases) showed a significantly increased MM risk in men with Empirical Dietary Inflammatory Pattern.

Methods: The NIH-AARP Diet and Health study is a prospective cohort of 567,169 persons who completed a food frequency questionnaire in 1995-1996 and were followed until December 2011. Healthy Eating Index-2015 (HEI-2015), Healthy Diet Score (HDS), alternate Mediterranean Diet (aMED) and healthful Plant-based Diet Index (hPDI) scores were calculated using *a priori* defined methods and grouped into quartiles, with higher scores reflecting healthier eating patterns. We prospectively evaluated the association between pre-diagnosis dietary patterns and MM incidence in this cohort. Hazard ratios (HR) and 95% confidence intervals (95%CI) were estimated using multivariate Cox proportional hazards models adjusted for age at study entry, sex, race, body mass index, education, and total energy intake (by residual method). Sensitivity analysis was conducted to assess reverse causality by excluding MM cases diagnosed within one year of follow-up.

Results: Among 392,589 participants (after exclusions), a total of 1,366 MM cases (59% males; 92% non-Hispanic whites) were identified during the follow-up period. Analysis revealed a significant association between hPDI scores and reduced MM risk (highest vs lowest quartile,

HR 0.85; 95%CI 0.73-1.0; p=0.043) (Table). In sensitivity analysis (1,302 MM cases), the association was no longer significant (HR 0.87; 95%CI 0.74-1.03; p 0.09) but trended in the same direction. This may be due to small sample size, given MM is a rare disease. HEI-2015, HDS and aMED scores were not associated with MM risk.

Conclusions: A healthful plant-based diet was associated with reduced MM risk in the NIH-AARP cohort. These results will help oncologists and patients make informed choices about their diet. To our knowledge, this is the largest epidemiologic study to date assessing pre-diagnosis dietary patterns and MM risk.

89 **Manuscript**

90 The incidence of multiple myeloma (MM), the second most common hematologic malignancy,
91 is rising globally [1]. Therefore, research efforts focused on identifying risk factors to reduce risk
92 of MM are essential. Several risk factors have been identified, some that are non-modifiable
93 (older age, male sex, African American race) and others that are modifiable (obesity, dietary
94 patterns, diabetes mellitus). Additionally, amongst 421 patients with plasma cell disorders, 82%
95 had questions about their diet and 57% reported their questions were not addressed by their
96 oncologists. Among those who received dietary guidance from their oncologists, 94%
97 attempted to follow it [2].
98
99 Despite this, there is limited data on dietary patterns and MM risk with few MM cases in each
100 study. The EPIC-Oxford cohort and Oxford Vegetarian study (65 MM cases) showed vegetarians
101 and vegans had 77% lower relative risk to develop MM than meat eaters [Relative risk (RR)
102 0.23, 95% confidence interval (95%CI) 0.09-0.59] [3]. The Nurses' Health Study and Health
103 Professionals Follow-up Study (478 MM cases) showed the Empirical Dietary Inflammatory
104 Pattern had a 16% increased MM risk in men [Hazard Ratio (HR) 1.16, 95%CI 0.96-1.24] [4].
105
106 Therefore, we evaluated the association between pre-diagnosis dietary patterns and MM risk in
107 the NIH-AARP Diet and Health Study, a large population-based, prospective cohort study. To
108 our knowledge, this is also the largest epidemiologic study on diet and MM risk to date with 1
109 366 MM cases.
110

In 1995-1996, a food frequency questionnaire was mailed to 3.5 million American Association of Retired Persons (AARP) members who were aged 50–71 years, residents of six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or two metropolitan areas (Atlanta and Detroit) [5]. A total of 566 398 satisfactorily completed questionnaires were returned between October 1995 and February 1997. Records were excluded from our analysis if they were completed in duplicate (n=179), questionnaire was completed by a proxy respondent (n=15 760) or proxy variable was not available or unknown (56 134), or if the participant died or moved out of the study area before returning the questionnaire (n=582), withdrew from the study (n=1), had a history of cancer as determined by self-report or confirmed from registry data (n=77 805), had a cancer diagnosis date prior to enrollment (n=1 564) and or had implausible energy intake (<800 or >4200 kcal/d for men and <600 or >3500 kcal/d for women) (n=20 967). After these exclusions, our final baseline cohort included 392 589 participants.

Study participants were followed from the date the questionnaire was received until first cancer diagnosis or until participant moved out of study area or died or follow-up period ended on December 31, 2011. Incident MM cases were identified through linkage to state cancer registries. Case ascertainment has been estimated to be about 90% complete [6]. MM cases were defined per International Classification of Diseases for Oncology, Third Edition code (ICD-O-3).

In this analysis, we used four dietary indices – Healthy Eating Index-2015 (HEI-2015), Healthy Diet Score (HDS), alternate Mediterranean Diet (aMED), and healthful Plant-based Diet Index (hPDI), to assess diet quality. Many of these scores have been inversely associated with cancer risk and cancer mortality. However, these pre-diagnosis scores have not been evaluated for MM risk. Using MyPyramid Equivalents Database and other variables, we were able to calculate each component and index scores for aMED and hPDI, while the HEI-2015 and HDS scores were previously calculated and provided in the database. These scores were grouped into quartiles. Higher scores imply higher adherence and a healthier diet.

The HEI-2015 is a measure of diet quality and overall alignment with the U.S. Dietary Guidelines for Americans and uses an energy-adjusted density approach for calorie adjustment [7]. There are nine adequacy components including total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acids. There are four moderation components including refined grains, sodium, added sugars, and saturated fats. The HEI score ranges from 0-100.

The HDS was adapted from the Healthy Diet Indicator which was based on World Health Organization recommendations [8]. It comprises of 12 components, saturated fatty acids, polyunsaturated fatty acids, protein, total carbohydrates, dietary fiber, fruit and vegetables, pulses and nuts, total non-milk extrinsic sugars, cholesterol, fish, red meat and meat products and calcium. Participants scored 0 or 1 based on their intake of each of these 12 items. The highest score is 11 [8].

The aMED score [9] was adapted from the traditional Mediterranean diet score [10] to assesses the conformity with the Mediterranean dietary pattern. The traditional Mediterranean Diet score was based on intake of nine components - vegetables, legumes, fruit and nuts, dairy, cereals, meat and meat products, fish, alcohol and the ratio of monounsaturated to saturated fat [10]. Intakes above the median received 1 point, all other intakes received 0 points. Meat and dairy product consumption less than median received 1 point. The aMED score excluded potato products from the vegetable group, separated fruit and nuts into 2 groups, eliminated the dairy group, included whole-grain products only, included only red and processed meats for the meat group and assigned alcohol intake between 5 and 15g/d for 1 point [9]. Scores ranged from 0 to 9.

The overall plant-based diet index (PDI) and hPDI were developed by splitting 18 dietary components into three groups: healthful plant foods (vegetables, whole grains, fruits, legumes, nuts, vegetable oils, tea/coffee), unhealthful plant foods (fruit juices, refined grains, potatoes, sugar sweetened beverages, sweets/desserts), and animal foods [11]. We utilized the hPDI, in which the highest score was given to the highest quintile of intake for each healthful food group available, and the lowest score given to the highest quintile of intake for unhealthful plant foods and animal foods available.

HR and 95%CI for MM risk in highest versus lowest quartiles of dietary index scores were estimated using multivariate Cox proportional hazards models with person-years as the

underlying time metric. The models were adjusted for age at study entry, sex, race (non-Hispanic Whites, non-Hispanic Blacks, other minority), body mass index (BMI) (<18.5, 18.5-24.9, 25-29.9, 30-34.9, ≥35), and education (less than high school, high school, post-high school training/college and unknown). Dietary variables were energy adjusted by residual method. Sensitivity analysis was conducted to assess reverse causality by excluding MM cases diagnosed within one year of follow-up.

Among 392,589 participants, 58.6% were males, 92.1% were non-Hispanic Whites, 34.4% had a normal BMI and 5.4% completed less than high school (Table 1). A total of 1 366 MM cases were identified during median follow-up period of 15.6 years. Multivariate analysis revealed a statistically significant inverse association between hPDI scores and MM risk (Q4 vs Q1, HR 0.85, 95%CI 0.73-1.0, p=0.043) (Table 2). There was no significant association between HEI-2015 (p=0.206), HDS (p=0.454), aMED (p=0.594) scores and MM risk. In a sensitivity analysis (1 302 MM cases), hPDI was associated with similar reduced MM risk statistical significance was not achieved (HR 0.87, 95%CI 0.74-1.03, p=0.09).

In this large prospective analysis of the NIH-AARP Diet and Health Study, we found that higher hPDI scores were associated with a reduced MM risk. HEI-2015, HDS and aMED scores were not significantly associated with MM risk. Our findings confirm the observations from the EPIC-Oxford and Oxford-Vegetarian study [3]. The Nurses' Health Study and Health Professionals Follow-up Study cohorts demonstrated 15-24% lower MM-specific mortality for presumed healthy pre-diagnosis plant-based dietary patterns [Alternate HEI (AHEI-2010), aMED, dietary

198 approaches to stop hypertension (DASH) and Prudent)] [HR range 0.76-0.85 per 1-standard
199 deviation (SD) increase in scores] and a 16-24% higher MM-specific mortality in unhealthy pre-
200 diagnosis dietary patterns (Western and inflammatory/insulinemic dietary patterns) (HR range
201 1.16-1.24, per 1-SD increase in scores) [12]. These findings also suggest that healthy pre-
202 diagnosis dietary habits may reduce risk of death once MM develops.
203
204 Plant-based diets are rich in fiber and phytochemicals and are associated with reduced cancer
205 risk and improved survival in cancer through multiple mechanisms such as improved BMI,
206 decreased inflammation, decreased insulin levels, decreased insulin-like growth factor 1 and
207 improved stool microbiome [13]. As the role of gut dysbiosis is being increasingly recognized in
208 the pathogenesis of MM, diet, the largest driver of microbiome composition can no longer be
209 ignored [14]. Preliminary results of a pilot nutrition-based intervention study (NUTRIVENTION)
210 in individuals with precursor plasma cell disorders and BMI ≥25 (NCT04920084) show that a
211 plant-based diet is feasible and leads to improvement in biomarkers associated with
212 progression to MM such as insulin resistance and gut microbiome composition [15]. A larger
213 randomized study of a plant-based diet is currently enrolling (NCT05640843) [16].
214
215 The strengths of this study include the large sample size of MM cases and prospective nature of
216 the study. A limitation of this study is the predominantly White population despite a higher MM
217 incidence in Blacks. Further studies are warranted to better understand the underlying
218 molecular and biological mechanisms.
219

In conclusion, the findings of this largest dietary epidemiologic study in MM are highly suggestive of a reduced MM risk with a healthful plant-based diet. These observations will help oncologists guide patients to make informed healthy dietary choices.

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Author Contributions

Concept and design: RP, FC, AD, UAS. Acquiring data: RP, FC, AD, UAS. Analyzing data: RP, FC, AD, JE, JMJ, UAS. Drafting the manuscript: RP, FC, JE, UAS. Critical revision of the manuscript: FC, RP, JMJ, AML, SZU, UAS. Approving the final version of the paper: FC, RP, JE, AD, JMJ, AML, SZU and UAS. Submission: RP and UAS. RP and FC contributed equally to this work. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability

The data that support the findings of this study are available from the NIH-AARP Diet and Health Study, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the NIH-AARP Diet and Health Study team.

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Table 1: Baseline characteristics of study cohort		
	Overall (N= 392,589)	**Multiple Myeloma (N=1366)**
Age at Entry		
>60	229,032 (58%)	952 (70%)
45-60	163,557 (42%)	414 (30%)
Sex		
Male	230,130 (59%)	961 (70%)
Female	162,459 (41%)	405 (30%)
Race		
Non-Hispanic White	361,486 (92%)	1,216 (89%)
Non-Hispanic Black	13,714 (4%)	94 (7%)
Hispanic/Asian/Pacific Islander/American Indian/Alaskan Native/Unknown	17,389 (4%)	56 (4%)
Body Mass Index		
<18.5	3,935 (1%)	11 (1%)
18.5-25	134,997 (34%)	420 (31%)
25-30	16,3455 (42%)	609 (45%)
30-35	59,669 (15%)	227 (17%)
>35	23,645 (6%)	75 (5%)
Education		
Less than high school	21,231 (5%)	74 (5%)
Completed high school	75,189 (19%)	248 (18%)
Post-high school training/ College/Postgraduate	286,512 (73%)	1,019 (75%)
Unknown	9,657 (3%)	25 (2%)

Table 2: Cox multivariate analysis for dietary pattern scores in quartiles and MM risk

Dietary Score	Q1	Q2	Q3	Q4	p-value
HEI-2015	1	1.15 (0.99, 1.34)	1.01 (0.87, 1.18)	1.01 (0.87, 1.19)	0.2055
HDS	1	0.95 (0.81, 1.10)	0.88 (0.76, 1.03)	0.92 (0.79, 1.07)	0.4537
aMED	1	1.02 (0.89, 1.18)	1.0 (0.87, 1.16)	0.92 (0.79, 1.07)	0.5942
hPDI	1	1.02 (0.88, 1.17)	1.05 (0.9, 1.23)	**0.85 (0.73, 1.00)**	**0.0429***

Hazard Ratio (95% confidence interval)
*Statistically significant
MM: Multiple myeloma; HEI-2015: Healthy Eating Index-2015; HDS: Healthy Diet Score; aMED: alternate Mediterranean Diet; hPDI: healthful Plant-based Diet Index; Q: Quartile.

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