Research Article

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Vegetarian Diets and the Incidence of Cancer in a Low-risk Population

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Abstract

Background: Cancer is the second leading cause of death in the United States. Dietary factors account for at least 30% of all cancers in Western countries. As people do not consume individual foods but rather combinations of them, the assessment of dietary patterns may offer valuable information when determining associations between diet and cancer risk.

Methods: We examined the association between dietary patterns (non-vegetarians, lacto, pesco, vegan, and semi-vegetarian) and the overall cancer incidence among 69,120 participants of the Adventist Health Study-2. Cancer cases were identified by matching to cancer registries. Cox proportional hazard regression analysis was conducted to estimate hazard ratios, with "attained age" as the time variable.

Results: A total of 2,939 incident cancer cases were identified. The multivariate HR of overall cancer risk among vegetarians compared with non-vegetarians was statistically significant [HR, 0.92; 95% confidence interval (CI), 0.85–0.99] for both genders combined. Also, a statistically significant association was found between vegetarian diet and cancers of the gastrointestinal tract (HR, 0.76; 95% CI, 0.63–0.90). When analyzing the association of specific vegetarian dietary patterns, vegan diets showed statistically significant protection for overall cancer incidence (HR, 0.84; 95% CI, 0.72–0.99) in both genders combined and for female-specific cancers (HR, 0.66; 95% CI, 0.47–0.92). Lacto-ovo-vegetarians appeared to be associated with decreased risk of cancers of the gastrointestinal system (HR, 0.75; 95% CI, 0.60–0.92).

Conclusion: Vegetarian diets seem to confer protection against cancer.

Impact: Vegan diet seems to confer lower risk for overall and female-specific cancer than other dietary patterns. The lacto-ovo-vegetarian diets seem to confer protection from cancers of the gastrointestinal tract. *Cancer Epidemiol Biomarkers Prev; 22(2); 286–94. ©2012 AACR.*

Introduction

Cancer is the leading cause of death worldwide (1) and the second leading cause of death in the United States, exceeded only by heart disease. According to the American Cancer Society, about 1,638,910 new cancer cases are expected to be diagnosed in 2012 and about 577,190 Americans are expected to die of cancer, more than 1,500 people a day (2).

It is estimated that more than half of all cancer cases and deaths worldwide are potentially preventable. Diet and nutrition are estimated to account for approximately 30% of all cancers in developed countries and 20% in developing countries (3). Dietary patterns allow estimates of disease associations beyond those for single food items or nutrients and include the total diet (4). Several studies (5–11) have been published that address the relationship between dietary factors and total cancer risk. It has been suggested that vegetarian diets are inversely related to overall cancer incidence (9), although not all studies agree. In addition, many results for specific cancers are inconsistent between studies. This lack of clarity may result from the heterogeneity of vegetarian diets between subjects and in different countries, as they may range greatly in the ratio of animal to plant food eaten, the quality of food, cooking methods, the limitations of measures used to quantify dietary intake, as well as other associated lifestyle factors that may produce an impact on the risk of cancer (10, 12).

To our knowledge, there are no prospective studies that have examined the association of more specific vegetarian subtypes (lacto-ovo-vegetarian, pesco-vegetarians, and vegans), semi-vegetarian and non-vegetarian diets, and overall cancer incidence. Thus, we sought to investigate the association of dietary patterns and cancer incidence in a low-risk population of men and women who participated in the Adventist Health Study-2 (AHS-2). Adventists comprise a study population with a large range of

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dietary habits that provides an uncommon unique opportunity for investigating dietary determinants of cancer.

We present here data and results concerning associations between dietary patterns and overall or broad groupings of incident cancers in this population. This preliminary work precedes analyses of site-specific cancers as we await longer follow-up to provide additional numbers of cancers and adequate statistical power for such analyses.

Materials and Methods

Subjects

AHS-2 is a prospective cohort study that includes 96,000 subjects. As matching to find incident cancers has as yet been conducted in only 38 U.S. states and Washington D. C. for a portion of the follow-up time, this reduces the number of subjects available for these analyses to 69,120 participants.

The AHS-2 began in 2002 as a study among Adventist church members throughout the United States and Canada. The scope of the AHS-2 is to investigate the role of various foods and nutrients, other lifestyle factors, and metabolic risk indicators that may be involved in cancer causation. Details of how members of this study were identified and how their dietary and other data were obtained have been described elsewhere (13).

Dietary assessment

Dietary intake was assessed with the use of a validated self-administered mailed food frequency questionnaire (FFQ; ref. 14). The FFQ contains a list of more than 200 food items including fruits, vegetables, legumes, grains, oils, dairy products including eggs, meats (red meat, poultry, and fish), beverage, and commercially prepared products such as dietary supplements, dry cereals, meat substitutes, and soy milk. Participants were asked to report their average frequency of intake and serving size during the past year, using predefined frequency categories according to the food under evaluation. Food variables that were of interest for this analysis included: red meat, poultry, fish, eggs, and dairy products. The frequency categories for all red meat, poultry, and fish variables ranged from "never or rarely" to "2+times per day" and from "never or rarely" to "6+ times per day" for dairy products. For serving size, 3 possible categories were available: standard, half or less, and half or more. Information on the intake of meat, fish, and dairy was used to categorize subjects according to their vegetarian status. The meat variable was the composite of red meat (hamburger, ground beef, processed beef, and lamb) and poultry (chicken, turkey, processed chicken, or turkey). Fish included salmon, white fish, tuna, and other fish. The dairy variable was the composite of cheddar cheese, butter, milk, low-fat milk, cottage cheese, cream cheese, low-fat cheese, evaporated milk, regular yogurt, low-fat yogurt, other dairy product, ice cream, ice milk, meal replacement drink, and hot chocolate. Thus, the following classification was obtained to assess vegetarian status: vegan, lacto-ovo-vegetarians, pesco-vegetarian, semi-vegetarian, and non-vegetarian. Vegans ate red meat, poultry, fish, eggs, and dairy <1 per month; lacto-ovo-vegetarians ate red meat, poultry, and fish <1 per month, and eggs and dairy $\geq$1 per month; pesco-vegetarians consumed red meat and poultry <1 per month, and fish $\geq$1 per month; semi-vegetarians ate red meat, poultry, fish 1 per month to 1 per week, and eggs or dairy at any level; and non-vegetarians, red meat, poultry, fish >1 per week, and eggs or dairy at any level.

This questionnaire also included questions about demographic characteristics, past medical history, family history of cancer, and lifestyle factors including exercise, smoking status, and alcohol intake.

Cancer ascertainment

Cancer cases were identified by computer matching of AHS-2 study members to state tumor registries. At this time, matches have been made with the following states: AK, AL, AR, AZ, CA, CO, CT, Washington DC, DE, FL, HI, IA, IL, IN, KS, KY, MA, MD, MI, MN, MT, MS, NC, ND, NE, NJ, NY, OH, OK, OR, PA, RI, SC, TX, UT, VT, VA, WA, and WY.

New cases of overall cancers comprised only the first malignancy diagnosed during the follow-up period and subjects with previous cancers were excluded from analyses. Cancer site was identified using the International Classification of Diseases-10 (ICD-10-CM; ref. 15). All new cancer cases were evaluated with exception of non-melanoma skin cancer. Cancers were also grouped by anatomical system but only digestive (C15–C26), respiratory and intra-thoracic (CC30–C39), urinary tract (C64–C68), female cancers (C50–C58), and male cancers (C60–C63) were assessed in this study. Cancer cases of a specific anatomic system were included if they were the first malignancy occurred for that specific group but not necessarily the first overall malignancy diagnosed during the study period. The definition of cancer in each anatomic system is provided in a footnote to Table 4.

Statistical analysis

The statistical package SAS, version 9.2 was used for the analyses of this study. Guided imputation (16) was used for the small amount of missing data in the dietary variables used for this study.

Sociodemographic characteristics of the population under study were presented after standardization by age, gender, and race (17). Person-years of follow-up time were calculated from the date of the baseline questionnaire until the date of a cancer diagnosis, death, relocation outside the above-named registry areas, or date that complete data were available at the registry of state of residence, whichever occurred first. Attained age was the time variable and all Cox proportional hazard models were left-censored.

Univariate analysis was conducted initially to evaluate the association between individual potential predictor factors and the overall cancer incidence. Multivariate Cox

regression models were developed to estimate cancer HRs and 95% confidence intervals (CI). A basic model that included the dependent variables of interest, gender, race, and education was built first. Other candidate covariates were selected on the basis of review of the literature and added to the basic model. The final model included the basic model plus paternal and/or maternal family history of cancer, smoking habits, alcohol intake, and female variables (age at menarche, pregnancies, menopausal status, use of hormone replacement therapy, and oral contraceptives). The final multivariate hazard rates and confidence intervals came from 5 independent datasets with imputed originally missing dietary data and were obtained using means of the 5 sets of β coefficients, and the required functions of the corresponding within- and between-dataset variances (18).

Cox proportional hazards multivariable analyses were developed for the incidence of overall cancers and specific cancers according to the selected anatomic systems. Sex-specific analyses were conducted for the overall cancer incidence analyses, as necessary. Otherwise female-specific variables were nested within gender. Dietary patterns were assessed as both specific dietary patterns (non-vegetarian, lacto-vegetarian, pesco-vegetarian, semi-vegetarian, and vegan) or in other analyses as just vegetarian (latter 4 specific categories) or non-vegetarian.

Elevated body weight has been linked with increased risk of some cancers. The relationship between some site-specific cancers and obesity is probably complex, and the exact mechanisms whereby obesity elevates cancer risk are not clearly understood. However, as dietary patterns have a strong correlation with body mass index (BMI) and BMI may act as intermediate causal variable between diet and cancer risk, for this study, final multivariate HRs were reported both for models excluding and including BMI.

Results

During 285,978 person-years or an average of 4.14 years of follow-up, we identified 2,939 cancer cases in both men and women.

Baseline characteristics of the study population according to incident cancer status are presented in Table 1. The median age of cancer diagnosis in this population was 59 years. Cancer cases were older and were more likely to have a positive family history of cancer. A higher proportion of men than women developed incident cancer. Cases also tended to have a higher BMI, less education, were less physically active, had slightly less frequent consumption of alcohol, but more commonly had a history of smoking.

Age, gender-, and race-standardized sociodemographic characteristics of the study population according to dietary pattern are shown in Table 2. A higher proportion of females were non-vegetarians than males. Non-vegetarians were younger, whereas pesco-vegetarians were older. As compared with Whites, Blacks were more likely to adopt pesco-vegetarian and non-vegetarian diets. Non-vegetarians were less educated, whereas lacto-ovo-vegetarians had the highest level of education. Large differences were observed in BMI with non-vegetarians having higher BMI (mean = 28.6 kg/m^2) than all vegetarian groups (mean = 25.8 kg/m^2) and vegans having the lowest proportion of overweight and obese participants. The mean BMI observed among the specific vegetarian groups were 24.0 kg/m^2 for vegans; 25.9 kg/m^2 for lacto-vegetarians, 26.12 kg/m^2 for pesco-vegetarians, and 27.1 kg/m^2 for semi-vegetarians. Non-vegetarians were more likely to have ever consumed alcohol or smoked cigarettes, and lacto-ovo-vegetarians were the least likely. As compared with other vegetarian groups, a higher proportion of non-vegetarians reported ever use of oral contraceptives and hormone replacement therapy whereas vegans had the lowest proportions.

Table 3 shows the age-adjusted HRs as well as multivariate HRs and 95% CIs of overall cancer risk by

Table 1. Sociodemographic and lifestyle characteristics of the participants of the AHS-2, according to incident cancer status

Variable	Cancer (%)	No incident cancer (%)	*P*
Gender			
Male	5.05	94.95	<0.0001
Female	3.81	96.19	
Age, y			
30–50	1.47	98.53	<0.0001
51–70	4.32	95.68	
71+	7.79	92.21	
Race			
White	4.41	95.59	0.0003
Black	3.77	96.23	
Education			
≤High School	4.77	95.23	0.0002
Some college	4.16	95.84	
College grad+	4.09	95.91	
BMI, kg/m^2			
<25	4.12	95.88	0.02
25–30	4.54	95.46	
≥31	4.07	95.93	
Family history			
Yes	5.26	94.74	<0.0001
No	3.70	96.30	
Alcohol			
Ever	3.97	96.03	0.002
Never	4.45	95.55	
Smoking			
Ever	4.73	95.27	0.002
Never	4.13	95.87	
Exercise			
Low	4.71	95.29	0.001
Medium	4.33	95.67	
High	3.99	96.01	

Table 2. Age-, gender-, race-adjusted sociodemographic and lifestyle characteristics of the participants of the AHS-2 by dietary patterns

Variable	Non-vegetarian	Lacto-vegetarian	Pesco-vegetarian	Semi-vegetarian	Vegan	*P*
Gender						
Male	35.66	36.24	33.89	31.09	36.94	<0.0001
Female	64.34	63.76	66.11	68.91	63.06	
Age, y						
30–50	33.39	29.79	26.69	29.72	29.55	<0.0001
51–70	45.76	43.58	44.48	42.91	46.28	
71+	20.85	26.63	28.83	27.37	24.17	
Race						
White	68.60	87.48	64.95	83.59	80.38	<0.0001
Black	31.40	12.52	35.05	16.41	19.62	
Education						
≤High school	25.12	14.53	19.38	22.04	17.47	<0.0001
Some college	30.17	24.32	25.88	27.63	37.86	
College grad+	44.71	61.15	54.74	50.33	44.67	
BMI, kg/m^2						
<25	30.73	47.66	48.21	39.42	65.31	<0.0001
25–30	37.33	33.87	35.10	36.79	24.30	
≥31	31.94	18.47	16.69	23.79	10.38	
Family history						
Yes	34.58	37.82	34.15	35.68	35.64	<0.0001
No	65.42	62.18	65.85	64.32	64.36	<0.0001
Alcohol						
Ever	48.36	27.85	37.55	39.17	34.31	<0.0001
Never	51.64	72.15	62.45	60.83	65.69	
Smoking						
Ever	25.58	12.27	16.80	19.99	15.86	<0.0001
Never	74.42	87.73	83.20	81.01	84.14	
Exercise						
Low	21.55	19.80	18.97	20.20	17.46	<0.0001
Medium	32.58	35.69	32.87	34.99	37.86	
High	45.87	44.51	48.16	44.81	44.67	
OC						
Ever	38.67	36.67	36.48	39.73	32.27	<0.0001
Never	61.33	63.33	63.52	60.27	67.73	
HRT						
Ever	22.43	20.39	20.95	23.80	16.24	<0.0001
Never	77.58	79.61	79.05	76.20	83.76	
Menopausal						
Menopausal/ Post-menopausal	51.28	52.44	50.96	52.34	52.52	<0.0001
Status						
Pre-menopausal	48.72	47.56	49.04	47.66	47.48	

NOTE: Standardized as appropriate.

vegetarian status, stratified by sex, with adjustment for race, family history of cancer, education, smoking, alcohol, age at menarche, pregnancies, breastfeeding, use of oral contraceptives, hormone replacement therapy, and menopause status. Vegetarian diets confer some protective association for the risk of overall cancer (HR, 0.92; 95% CI, 0.85–0.99). However, in sex-specific analyses, no significance was obtained for either males or females separately.

When analyzing the association of dietary patterns (see Table 3) with overall cancer risk, only vegan diets showed a statistically significant protective association ($P = 0.03$) when both sexes are combined. This protection seems to be mainly in males on sex-specific analysis,

Table 3. Age-adjusted and multivariate-adjusted HR of the association between vegetarian status and specific dietary patterns and overall cancer incidence

	Dietary patterns					
	Non-vegetarian	**Vegetarian[a]**	**Lacto-vegetarian**	**Pesco-vegetarian**	**Semi-vegetarian**	**Vegan**
Both males and females						
Person at-risk	33,736	35,384	19,735	6,846	3,881	4,922
Number of events	1,413	1,526	878	276	182	190
Person-years	139,596.95	14,6381.72	80,858.84	29,128.40	15,830.39	20,564.08
HR[b] (95% CI)	Reference	0.91 (0.85–0.98)	0.94 (0.86–1.02)	0.84 (0.74–0.96)	1.001 (0.86–1.17)	0.83 (0.71–0.97)
HR[c] (95% CI)	Reference	0.92 (0.85–1.00)	0.95 (0.86–1.04)	0.89 (0.77–1.03)	0.98 (0.83–1.18)	0.86 (0.73–1.00)
HR[d] (95% CI)	Reference	0.92 (0.85–0.99)	0.93 (0.85–1.02)	0.88 (0.77–1.01)	0.98 (0.82–1.17)	0.84 (0.72–0.99)
P[e]		0.03	0.14	0.06	0.81	0.03
Males						
Person at-risk	11,813	12,633	7,275	2,301	1,226	1,831
Number of events	592	643	380	114	72	77
Person-years	47,990.38	51,141.14	29,317.07	9,480.37	4,798.89	7,544.81
HR[b] (95% CI)	Reference	0.89 (0.79–0.99)	0.90 (0.79–1.03)	0.82 (0.67–1.00)	1.10 (0.87–1.41)	0.77 (0.61–0.97)
HR[f] (95% CI)	Reference	0.92 (0.81–1.03)	0.92 (0.80–1.06)	0.88 (0.71–1.09)	1.11 (0.85–1.45)	0.81 (0.64–1.02)
HR[g] (95% CI)	Reference	0.90 (0.80–1.01)	0.91 (0.79–1.05)	0.87 (0.70–1.07)	1.09 (0.83–1.43)	0.79 (0.62–1.00)
P[e]		0.08	0.19	0.19	0.51	0.05
Females						
Person at-risk	21923	22751	12460	4545	2655	3091
Number of Events	821	883	498	162	110	113
Person-Years	91606.57	95240.58	51541.77	19648.03	11031.50	13019.27
HR[b] (95%CI)	Reference	0.93 (0.84–1.02)	0.96 (0.86–1.07)	0.85 (0.72–1.19)	0.98 (0.80–1.19)	0.88 (0.72–1.07)
HR[c] (95%CI)	Reference	0.93 (0.84–1.03)	0.96 (0.85–1.08)	0.90 (0.74–1.09)	0.92 (0.73–1.16)	0.91 (0.75–1.11)
HR[d] (95%CI)	Reference	0.92 (0.83–1.02)	0.95 (0.84–1.07)	0.94 (0.77–1.13)	0.92 (0.73–1.16)	0.93 (0.77–1.14)
p-value[e]		0.11	0.36	0.50	0.47	0.50

[a]Vegetarian group includes lacto-ovo-vegetarian, pesco-vegetarian, semi-vegetarian, and vegan.

[b]HR adjusted by age.

[c]HR adjusted by race, family history of cancer, BMI, education, smoking, alcohol, age at menarche, pregnancies, breastfeeding, oral contraceptives, hormone replacement therapy, and menopause status.

[d]HR adjusted by race, family history of cancer, education, smoking, alcohol, age at menarche, pregnancies, breastfeeding, oral contraceptives, hormone replacement therapy, and menopause status.

[e]*P* value for the multivariate HR without BMI.

[f]HR adjusted by race, family history of cancer, BMI, education, smoking, and alcohol.

[g]HR adjusted by race, family history, education, smoking, and alcohol.

although then not quite statistically significant (HR, 0.79; 95% CI, 0.62–1.003).

Multivariate analysis for cancers of different anatomic systems (Table 4) showed a protective association between vegetarians and cancer of the gastrointestinal tract (HR, 0.76; 95% CI, 0.63–0.90; $P = 0.002$). Further analysis showed that this protection was statistically significant in lacto-vegetarians (HR, 0.75; 95% CI, 0.60–0.93; $P = 0.009$). Although cancers specific to females were not significantly associated with vegetarian or non-vegetarian diets, a statistically significant protective association was observed for those who adhered to vegan diets (HR, 0.66; 95% CI, 0.47–0.92; $P = 0.01$). Pesco-vegetarian diet showed a decreased point estimate for the risk of cancer of the respiratory tract. However, no statistically significant association was achieved (HR, 0.53; 95% CI, 0.28–1.03; $P = 0.06$).

A set of similar multivariate models that included BMI as covariate were also examined. No important changes were identified for overall cancer risk among the different dietary patterns compared with the multivariate models without BMI. However, in these models, effects for all vegetarians (HR, 0.92; 95% CI, 0.85–1.00; $P = 0.05$) and vegans (HR, 0.86; 95% CI, 0.73–1.00; $P = 0.06$) achieved only borderline significance. When stratified by gender, again no important differences were observed in the HR for overall cancers among the different dietary patterns compared with analyses without BMI. The protective association conferred by vegetarian (HR, 0.77; 95% CI, 0.63–0.93; $P = 0.006$) and lacto-ovo-vegetarian (HR, 0.76; 95% CI, 0.61–0.94; $P =$

Table 4. Age-adjusted and multivariate-adjusted HR of anatomic cancer sites associated with vegetarian status and specific dietary patterns

Variables	Person at-risk	No. of events	Person-years	HR[a] (95% CI)	HR[b,c] (95% CI)	HR[d] (95% CI)	*P*[e]
GIT							
Non-vegetarian	33,736	260	142,083.07	1.00	1.00	1.00	
Vegetarian	35,384	235	149,249.07	0.72 (0.61–0.86)	0.76 (0.63–0.90)	0.77 (0.63–0.93)	0.002
Lacto-vegetarian	19,735	131	82,469.72	0.72 (0.58–0.89)	0.75 (0.60–0.93)	0.76 (0.61–0.94)	0.009
Pesco-vegetarian	6,846	46	29,672.61	0.73 (0.53–1.00)	0.78 (0.56–1.07)	0.79 (0.57–1.09)	0.13
Semi-vegetarian	3,881	23	16,208.05	0.64 (0.42–0.99)	0.73 (0.48–1.13)	0.74 (0.48–1.14)	0.16
Vegan	4,922	35	20,898.69	0.81 (0.57–1.15)	0.78 (0.54–1.13)	0.80 (0.55–1.17)	0.19
RT							
Non-vegetarian	33,736	98	142,366.02	1.00	1.00	1.00	
Vegetarian	35,384	72	149,517.29	0.59 (0.43–0.80)	0.77 (0.55–1.06)	0.75 (0.54–1.04)	0.11
Lacto-vegetarian	19,735	46	82,630.99	0.67 (0.47–0.96)	0.91 (0.63–1.33)	0.85 (0.61–1.30)	0.65
Pesco-vegetarian	6,846	10	29,719.82	0.42 (0.22–0.81)	0.53 (0.28–1.03)	0.52 (0.27–1.00)	0.06
Semi-vegetarian	3,881	8	16,218.93	0.60 (0.29–1.23)	0.73 (0.37–1.47)	0.72 (0.34–1.53)	0.38
Vegan	4,922	8	20,947.55	0.49 (0.24–1.00)	0.62 (0.30–1.28)	0.59 (0.28–1.23)	0.20
UT							
Non-vegetarian	33,736	79	142,366.40	1.00	1.00	1.00	
Vegetarian	35,384	115	149,379.29	1.16 (0.87–1.55)	1.17 (0.87–1.57)	1.21 (0.89–1.65)	0.30
Lacto-vegetarian	19,735	60	82,555.48	1.07 (0.77–1.51)	1.08 (0.76–1.54)	1.13 (0.79–1.61)	0.66
Pesco-vegetarian	6,846	17	29,704.93	0.88 (0.52–1.49)	0.88 (0.51–1.52)	0.93 (0.54–1.60)	0.65
Semi-vegetarian	3,881	18	16,205.68	1.66 (0.99–2.77)	1.56 (0.93–2.61)	1.59 (0.91–2.78)	0.09
Vegan	4,922	20	20913.20	1.51 (0.92–2.46)	1.57 (0.96–2.57)	1.73 (1.05–2.84)	0.07
MC							
Non-vegetarian	11,813	264	48588.34	1.00	1.00	1.00	
Vegetarian	12,633	289	51797.25	0.93 (0.78–1.10)	0.93 (0.42–2.06)	0.94 (0.42–2.07)	0.86
Lacto-vegetarian	7,275	171	29716.85	0.61 (0.78–1.15)	0.94 (0.77–1.15)	0.95 (0.66–1.25)	0.56
Pesco-vegetarian	2,301	54	9589.94	0.91 (0.68–1.22)	0.91 (0.66–1.25)	0.91 (0.66–1.26)	.56
Semi-vegetarian	1,226	30	4875.19	1.05 (0.72–1.53)	1.11 (0.75–1.64)	1.12 (0.76–1.65)	.59
Vegan	1,831	34	7615.27	0.78 (0.54–1.11)	0.81 (0.57–1.16)	0.81 (0.57–1.17)	.24
FC							
Non-vegetarian	21,923	387	92416.54	1.00	1.00	1.00	
Vegetarian	22751	414	96061.37	0.97 (0.84–1.11)	0.93 (0.81–1.07)	0.97 (0.84–1.13)	0.33
Lacto-vegetarian	12460	245	51972.44	1.05 (0.90–1.24)	1.01 (0.85–1.19)	1.04 (0.87–1.25)	0.92
Pesco-vegetarian	4545	74	19796.82	0.85 (0.67–1.09)	0.88 (0.69–1.12)	0.92 (0.71–1.19)	0.29
Semi-vegetarian	2655	56	11120.57	1.12 (0.85–1.48)	1.02 (0.74–1.40)	1.03 (0.75–1.42)	0.89
Vegan	3091	39	13171.54	0.66 (0.48–0.92)	0.66 (0.47–0.92)	0.71 (0.50–1.01)	0.01

Abbreviations: FC, all female cancer (female breast, vulva, vagina, cervix uteri, corpus uteri, endometrial, uterus, and ovary); GIT, cancer of the gastrointestinal tract (esophagus, stomach, small intestine, colon, liver and bile ducts, gallbladder, biliary tract, and pancreas); MC, all male cancer (prostate, penis, and testis); RT, cancer of the respiratory tract and intrathoracic organs (nasal cavity, middle ear, larynx, trachea, bronchus, lung, heart, mediastinum, and pleura); UT, cancer of the urinary tract (renal pelvis, ureter, kidney, and bladder).

[a]HR adjusted by age.

[b]Multivariate HR model adjusted by race, family history of cancer, education, smoking, alcohol, age at menarche, pregnancies, breastfeeding, oral contraceptives, hormone replacement therapy, and menopause status. This multivariate HR is applicable for all anatomic cancer sites except male-specific cancers.

[c]Multivariate HR model adjusted by race, family history of cancer, education, smoking, and alcohol. This multivariate HR is applicable only for male-specific cancers.

[d]Multivariate HR including BMI.

[e]*P* value for the multivariate HR without BMI.

0.001) diets remained and were statistically significant, for cancers of the gastrointestinal system. The point estimate for female-specific cancers among vegans (HR, 0.71; 95% CI, 0.50–1.01; $P = 0.06$) increased slightly compared with the analysis without BMI (HR, 0.66; 95% CI, 0.47–0.92; $P = 0.01$), perhaps supporting the idea that this diet acts, in part, through effects on BMI.

Multivariate models including energy intake as a covariate were also assessed but no important differences were observed in the HR for overall cancer and system-specific cancers according to dietary pattern.

Discussion

In this cohort, a clear association between vegetarianism (as a single category) and all cancers was found. This association was clearest in the vegan diet, where there was a mild protection for overall cancer risk. When dividing cancers to anatomic site or gender-specific groupings, some statistically significant associations were also found. Specifically vegetarians had less gastro-intestinal cancer (HR, 0.76), especially among lacto-ovo vegetarians (HR, 0.75). In addition, vegan women experienced fewer female-specific cancers (HR, = 0.66). It is also noteworthy that, although often not statistically significant, the great majority of HR point estimates for effects of vegetarian status or its subtypes are less than 1.0. Exceptions are only male semi-vegetarians (Table 3), lacto and semi-vegetarians in female-specific cancers and urinary tract cancers (Table 4). When adding BMI into the multivariate models, most of the statistically relative risks remain significant but move slightly toward the null, suggesting that BMI may be one mediator of the dietary effects.

Few prospective studies have looked at associations between vegetarian diets and cancer risk (8, 9, 19). Among the Seventh-day Adventist population, cancer risk for all sites combined (20) has been previously reported as lower than an external reference population. As many Adventists do not consume meat regularly, it is possible that low meat consumption, or the replacement sources of energy for the meat, would confer this protection. Furthermore, when exploring dietary associations with the risk of specific cancers, analyses in the older AHS-1 cohort data found evidence that meat consumption is directly associated with the risk of specific cancer sites and also that greater consumption of vegetables and fruits predicts lower risk of certain cancer sites (21). Further evidence comes from the pooled analysis of data from 2 prospective studies in the United Kingdom, namely, the Oxford Vegetarian Study and, the European Prospective Investigation into Cancer and Nutrition-Oxford (EPIC-Oxford) cohort where 12% decreased risk of overall cancer was observed among vegetarians compared with meat eaters after adjustment for potential confounding factors (8). However, associations between the vegan diet and cancer were not evaluated separately because of the small number of cancers reported.

A link has been suggested between specific plant foods such as fruits and vegetables, plant constituents such as fiber, antioxidants, other phytochemicals, maintaining a healthy weight and a lower incidence of cancer (22). Vegetarians and vegans generally include greater amounts of plant foods, avoid the intake of meat, and often adopt other healthy lifestyles than non-vegetarians (12). Thus, there is a reason to suspect that vegetarian diets may protect against cancer. Factors associated with the high fiber content in vegetarian diets promote increased insulin sensitivity (23). A cross-sectional study suggests, in addition, that a plant-based diet is associated with lower circulating levels of total insulin-like growth factor (IGF)-I and higher levels of IGF-binding protein (IGFBP)-I and IGFBP-2 compared with a meat-eating or even a lacto-ovo-vegetarian diet (24). Insulin and IGF-I act as promoters for most normal and preneoplastic tissues. Therefore, their downregulation may reduce cancer rates (25–27).

In our study, an inverse association was evident between vegan diets and female-specific cancers. Much of the known epidemiology of gynecologic and breast cancers can be explained by hormonal factors, and the only definite lifestyle effects on risks of these cancers are obesity, physical activity, and alcohol consumption (28). Vegan diets conceivably protect against cancers linked to obesity, elevated IGF-1 levels, and insulin resistance (25, 28). As there is evidence that obesity is a risk factor for several common female-specific cancers (29) and that high levels of IGF-I may also increase the risk of some female-specific cancers (30–32), these are potentially protective pathways.

Vegans also consume substantial amounts of soybeans or foods made from soybeans. Soy foods are rich in phytoestrogens which have been hypothesized to reduce breast cancer risk (28). Finally, the low intake of protein and the lower frequency of obesity in this group suggest a lower energy intake that may well delay the onset of menarche and also influence hormone status at other periods of life (33, 34).

Our results suggest that lacto-ovo-vegetarians compared with meat eaters are inversely associated with the development of cancers of the gastrointestinal system. Previous studies have strongly suggested that dairy foods are inversely associated with cancers of the digestive system in both men and women (5), this being especially so for colorectal cancer (5, 33, 35, 36). Similar effects for gastric (37–39), esophageal (39), and pancreatic (40) cancer are either controversial or absent. It is important to note that in those studies with null or positive (rather than negative) associations, high-fat dairy products were generally the main exposures of interest. Calcium has been shown to reduce proliferation, stimulate differentiation, and induce apoptosis in cells of the gastrointestinal tract (41).

No statistically significant associations between dietary patterns and cancers of the respiratory tract, urinary tract, and male cancers were observed. However, the point estimates, particularly in the pesco-vegetarian group, were in the protective direction for cancers of the respiratory and urinary system. Key and colleagues have reported similar inverse nonstatistically significant

associations between fish eaters and lung, kidney, and bladder cancer incidence (8). Further investigation is necessary with larger numbers in the future and also when considering specific cancers.

The major strength of our study is its prospective design and the validation of new cancers through cancer registries. Also, the unique lifestyle of the Adventist population with a wide variety of dietary habits, a very low percentage of alcohol consumption or cigarette smoking, reduces the possibility of confounding by these nondietary factors.

The potential limitations of our study include unavoidable inaccuracies in the assessment of food consumption. It is likely that participants may have overestimated some foods generally considered beneficial due to social desirability. However, this type of misclassification should be nondifferential, usually biasing the results toward the null. Furthermore, our published data (14) comparing questionnaire with six 24-hour dietary recall data suggest good validity for the foods used to determine the vegetarian categories.

The non-vegetarian reference group in AHS-2 was relatively low meat consuming. Thus, if diets mainly based on animal products provide an adverse effect, it is possible that the relatively low animal product intake of the non-vegetarians in this cohort could result in smaller observed effects. Low numbers, as yet, for pesco-vegetarians, semi-vegetarians, and vegans, limit our conclusions. Finally, although we did adjust for many potential risk factors available in our study for site-specific cancer, residual confounding by unknown or unmeasured risk factors may exist for some cancers.

In conclusion, this study suggests that vegan diets may be associated with a decrease in the incidence of all cancers combined and specifically the risk of female-specific cancers when compared with non-vegetarians. Vegetarians (mainly lacto-ovo-vegetarians) as a combined group have lower risk of all cancers and gastrointestinal cancers than meat eaters.

Disclosure of Potential Conflicts of Interest

The results reported here and the conclusions based on them are the sole responsibility of the authors. No potential conflicts of interest were disclosed.

Authors' Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Jaceldo-Siegl, G. Fraser
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Tantamango-Bartley, J. Fan, G. Fraser
Writing, review, and/or revision of the manuscript: Y. Tantamango-Bartley, K. Jaceldo-Siegl, G. Fraser
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Tantamango-Bartley
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