Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2013 February ; 22(2): 286–294. doi: 10.1158/1055-9965.EPI-12-1060.

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 US. Dietary factors account for at least 30% of all cancers in Western countries. Since 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 performed to estimate hazard ratios, with "attained age" as the time variable.

Results—2,939 incident cancer cases were identified. The multivariate HR of overall cancer risk among vegetarians compared to non-vegetarians was statistically significant (HR=0.92; 95%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 compared to other dietary patterns. The lacto-ovo-vegetarian diets seem to confer protection from cancers of the gastrointestinal tract.

Keywords

cancer; vegetarian dietary patterns; diet; vegan; lacto-ovo-vegetarians

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Conflict of Interest: Authors declare no conflict of interest

The results reported here and the conclusions based on them are the sole responsibility of the authors.

INTRODUCTION

Cancer is the leading cause of death worldwide (1) and the second leading cause of death in the United States (US), 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 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 DC 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 USA 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).(14) The FFQ contains a list of over 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, ½ or less and ½ 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 ≥ 1 per month; pesco-vegetarians consumed red meat and poultry < 1 per month, and fish ≥ 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: Alaska, Alabama, Arkansas, Arizona, California, Colorado, Connecticut, Washington DC, Delaware, Florida, Hawaii, Iowa, Illinois, Indiana, Kansas, Kentucky, Massachusetts, Maryland, Michigan, Minnesota, Montana, Mississippi, North Caroline, North Dakota, Nebraska, New Jersey, New York, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Caroline, Texas, Utah, Vermont, Virginia, Washington, and Wyoming.

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).(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 anatomical 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 anatomical 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.

Socio-demographic 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 was 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 performed initially to evaluate the association between individual potential predictor factors and the overall cancer incidence. Multivariate cox-regression models were developed to estimate cancer hazard ratios (HR) 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 based on 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 five independent datasets with imputed originally missing dietary data, and were obtained using means of the five 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 anatomical systems. Sex-specific analyses were performed 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 four 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 since dietary patterns have a strong correlation with 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 old. 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 socio-demographic characteristics of the study population according to dietary pattern are shown in Table 2. A higher proportion of females were non-vegetarians compared to males. Non-vegetarians were younger while pesco-vegetarians were older. As compared to 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=28.6Kg/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; 25.9Kg/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 to 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 hazard ratios (HR) as well as multivariate HR and 95% confidence intervals (95% CI) of overall cancer risk by 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-value=0.03) when both sexes are combined. This protection seems to be mainly in males on sex-specific analysis, 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 to the multivariate models without BMI. However, in these models effects for all vegetarians (HR=0.92; 95%CI: 0.85–1.00, p=.05) and vegans (HR=0.86; 95%CI: 0.73–1.00; p=.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 to analyses without BMI. The protective association conferred by vegetarian (HR=0.77; 95% CI: 0.63–0.93; p=.006) and lacto-ovo-vegetarian (HR=0.76; 95% CI: 0.61–0.94; p=.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=.06) increased slightly compared to the analysis without BMI (HR=0.66; 95%CI: 0.47–0.92; p=.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 anatomical 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 hazard ratio point estimates for effects of vegetarian status or its sub-types 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. Since 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 two 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 to 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 compared to non-vegetarians.(12) Thus there is 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 IGF-I and higher levels of 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 pre-neoplastic tissues. Therefore, their down- regulation 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 soy beans. 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, suggests 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 to 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 non-statistically 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 non-dietary 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 non-differential, usually biasing the results toward the null. Further our published data(14) comparing questionnaire with six 24-hour dietary recall data suggests 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.

Acknowledgments

Financial Support: This study was funded as part of the NIH, the USDA and the WCRF grants received by the AHS-2

Cancer incidence data have been provided by the “Alaska Cancer Registry”, “Alabama State Cancer Registry”, “Arizona Cancer Registry”, “Arkansas Cancer Registry”, “California Cancer Registry”, “Colorado Cancer Registry”, “Connecticut Tumor Registry”, “District of Columbia Cancer Registry, District of Columbia Department of Health”, “Delaware Cancer Registry”, “Florida Cancer Data System”, “Hawaii Tumor registry”, “Iowa Cancer Registry”, “Illinois State Cancer Registry”, “Indiana State Department of Health”, “Kansas Cancer Registry”, “Kentucky Cancer Registry”, “Mississippi Cancer Registry”, “Maryland Cancer Registry, Center for Cancer Surveillance & Control, Dept. of Health & Mental Hygiene”, “Michigan’s Cancer Registry”, “Minnesota Cancer Surveillance System”, “Montana Central Tumor Registry, Montana Department of Public Health & Human

Services", "North Carolina State Center for Health Statistics", "North Dakota Statewide Cancer Registry", "Nebraska Dept. of Health & Human Services & Its medical record & Health information registries", "New Jersey State Cancer Registry", "New York State Cancer Registry", "Ohio Cancer Registrar Association", "Oklahoma Central Cancer Registry, Oklahoma State Department of Health", "Oregon State Cancer Registry", "Bureau of Health Statistics & Research, Pennsylvania Department of Health", "Rhode Island Cancer Registry", "South Carolina Cancer Registry", "Texas Cancer Registry", "Utah Department of Health", "Vermont Cancer Registry", "Virginia Cancer Registry", "Washington State Cancer Registry", "Wyoming Cancer Surveillance System".

Grant Support

NIH – "Plant-based diet and risk of cancer" 1UO1 CA 152939

USDA – "Nutrition, diet and lifestyle research for longevity and healthy aging" 2010-38938-20924

WCRF – "Dairy meat, linoleic acid and soy consumption as risk factors for prostate, colorectal, and breast cancer in a cohort with a wide range of dietary habits: Adventist Health Study-2" 2009/93

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TABLE 1

Socio-demographic and lifestyle characteristics of the participants of the Adventist Health Study- 2, according to incident cancer status.

Variable		Cancer (%)	No incident cancer (%)	p-value
Gender	Male	5.05	94.95	<.0001
	Female	3.81	96.19	
Age	30–50 years	1.47	98.53	<.0001
	51–70 years	4.32	95.68	
	71+ years	7.79	92.21	
Race	White	4.41	95.59	.0003
	Black	3.77	96.23	
Education	≤High School	4.77	95.23	.0002
	Some College	4.16	95.84	
	College grad+	4.09	95.91	
BMI	<25 kg/m^2	4.12	95.88	.02
	25–30 kg/m^2	4.54	95.46	
	>=31 kg/m^2	4.07	95.93	
Family History	Yes	5.26	94.74	<.0001
	No	3.70	96.30	
Alcohol	Ever	3.97	96.03	.002
	Never	4.45	95.55	
Smoking	Ever	4.73	95.27	.002
	Never	4.13	95.87	
Exercise	Low	4.71	95.29	.001
	Medium	4.33	95.67	
	High	3.99	96.01	

TABLE 2

Age-gender-race Adjusted[a] Socio-demographic and lifestyle characteristics of the participants of the Adventist Health Study- 2 by dietary patterns.

Variable		Non-Vegetarian	Lacto-Vegetarian	Pesco-Vegetarian	Semi-Vegetarian	Vegan	*P*-value
Gender	Male	35.66	36.24	33.89	31.09	36.94	<.0001
	Female	64.34	63.76	66.11	68.91	63.06	
Age	30–50 years	33.39	29.79	26.69	29.72	29.55	<.0001
	51–70 years	45.76	43.58	44.48	42.91	46.28	
	71+ years	20.85	26.63	28.83	27.37	24.17	
Race	White	68.60	87.48	64.95	83.59	80.38	<.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	<.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	<25 kg/m^2	30.73	47.66	48.21	39.42	65.31	<.0001
	25–30 kg/m^2	37.33	33.87	35.10	36.79	24.30	
	>=31 kg/m^2	31.94	18.47	16.69	23.79	10.38	
Family	Yes	34.58	37.82	34.15	35.68	35.64	<.0001
History	No	65.42	62.18	65.85	64.32	64.36	<.0001
Alcohol	Ever	48.36	27.85	37.55	39.17	34.31	<.0001
	Never	51.64	72.15	62.45	60.83	65.69	
Smoking	Ever	25.58	12.27	16.80	19.99	15.86	<.0001
	Never	74.42	87.73	83.20	81.01	84.14	
Exercise	Low	21.55	19.80	18.97	20.20	17.46	<.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	<.0001
	Never	61.33	63.33	63.52	60.27	67.73	
HRT	Ever	22.43	20.39	20.95	23.80	16.24	<.0001
	Never	77.58	79.61	79.05	76.20	83.76	
Menopausal Status	Menopausal/Post-menopausal	51.28	52.44	50.96	52.34	52.52	<.0001
	Pre-menopausal	48.72	47.56	49.04	47.66	47.48	

[a] Standardized as appropriate

TABLE 3

Age-adjusted and multivariate adjusted hazard ratio (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	33736	35384	19735	6846	3881	4922
Number of Events	1413	1526	878	276	182	190
Person-Years	139596.95	146381.72	80858.84	29128.40	15830.39	20564.08
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-value[e]		.03	.14	.06	.81	0.03*
	MALES					
Person at risk	11813	12633	7275	2301	1226	1831
Number of Events	592	643	380	114	72	77
Person-Years	47990.38	51141.14	29317.07	9480.37	4798.89	7544.81
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-value[e]		.08	.19	.19	.51	.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]		.11	.36	.50	.47	.50

NOTE: P-Y: Person-Years; IR: Incidence Rate; HR: Hazard Ratio; CI: Confidence Interval

[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.

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2014 February 01.

TABLE 4

Age-adjusted and Multivariate adjusted hazard ratio of anatomical cancer sites associated with vegetarian status and specific dietary patterns.

Variables	Person at risk	# Events	Person-Years	HR[a] (95%CI)	HR[b,c] (95%CI)	HR[d] (95%CI)	*p*-value[e]
GIT							
Non – Vegetarian	33736	260	142083.07	1.00	1.00	1.00	
Vegetarian	35384	235	149249.07	0.72 (0.61 – 0.86)	0.76 (0.63 – 0.90)	0.77 (0.63 – 0.93)	0.002
Lacto – vegetarian	19735	131	82469.72	0.72 (0.58 – 0.89)	0.75 (0.60 – 0.93)	0.76 (0.61 – 0.94)	.009
Pesco - vegetarian	6846	46	29672.61	0.73 (0.53 – 1.00)	0.78 (0.56 – 1.07)	0.79 (0.57 – 1.09)	.13
Semi-vegetarian	3881	23	16208.05	0.64 (0.42 – 0.99)	0.73 (0.48 – 1.13)	0.74 (0.48 – 1.14)	.16
Vegan	4922	35	20898.69	0.81 (0.57 – 1.15)	0.78 (0.54 – 1.13)	0.80 (0.55 – 1.17)	.19
RT							
Non – Vegetarian	33736	98	142366.02	1.00	1.00	1.00	
Vegetarian	35384	72	149517.29	0.59 (0.43 – 0.80)	0.77 (0.55 – 1.06)	0.75 (0.54 – 1.04)	0.11
Lacto – vegetarian	19735	46	82630.99	0.67 (0.47 – 0.96)	0.91 (0.63 – 1.33)	0.85 (0.61 – 1.30)	.65
Pesco - vegetarian	6846	10	29719.82	0.42 (0.22 – 0.81)	0.53 (0.28 – 1.03)	0.52 (0.27 – 1.00)	.06
Semi – vegetarian	3881	8	16218.93	0.60 (0.29 – 1.23)	0.73 (0.37 – 1.47)	0.72 (0.34 – 1.53)	.38
Vegan	4922	8	20947.55	0.49 (0.24 – 1.00)	0.62 (0.30 – 1.28)	0.59 (0.28 – 1.23)	.20
UT							
Non – Vegetarian	33736	79	142366.40	1.00	1.00	1.00	
Vegetarian	35384	115	149379.29	1.16 (0.87 – 1.55)	1.17 (0.87 – 1.57)	1.21 (0.89 – 1.65)	0.30
Lacto – vegetarian	19735	60	82555.48	1.07 (0.77 – 1.51)	1.08 (0.76 – 1.54)	1.13 (0.79 – 1.61)	.66
Pesco - vegetarian	6846	17	29704.93	0.88 (0.52 – 1.49)	0.88 (0.51 – 1.52)	0.93 (0.54 – 1.60)	.65
Semi – vegetarian	3881	18	16205.68	1.66 (0.99 – 2.77)	1.56 (0.93 – 2.61)	1.59 (0.91 – 2.78)	.09
Vegan	4922	20	20913.20	1.51 (0.92 – 2.46)	1.57 (0.96 – 2.57)	1.73 (1.05 – 2.84)	.07
MC							
Non -Vegetarian	11813	264	48588.34	1.00	1.00	1.00	
Vegetarian	12633	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	7275	171	29716.85	0.61 (0.78 – 1.15)	0.94 (0.77 – 1.15)	0.95 (0.66 – 1.25)	.56
Pesco – vegetarian	2301	54	9589.94	0.91 (0.68 – 1.22)	0.91 (0.66 – 1.25)	0.91 (0.66 – 1.26)	.56
Semi – vegetarian	1226	30	4875.19	1.05 (0.72 – 1.53)	1.11 (0.75 – 1.64)	1.12 (0.76 – 1.65)	.59
Vegan	1831	34	7615.27	0.78 (0.54 – 1.11)	0.81 (0.57 – 1.16)	0.81 (0.57 – 1.17)	.24

Variables	Person at risk	# Events	Person-Years	HR[a] (95%CI)	HR[b,c] (95%CI)	HR[d] (95%CI)	*p*-value[e]
FC							
Non – Vegetarian	21923	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)	.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)	.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)	.89
Vegan	3091	39	13171.54	0.66 (0.48 – 0.92)	0.66 (0.47 – 0.92)	0.71 (0.50 – 1.01)	.01

NOTE: P-Y: Person-Years; IR : Incidence Rate; HR: Hazard Ratio; CI: Confidence Interval

GIT includes cancer of the gastrointestinal tract which includes: esophagus, stomach, small intestine, colon, liver and bile ducts, gallbladder, biliary tract, pancreas

RT includes cancer of the respiratory tract and intra-thoracic organs which includes: nasal cavity, middle ear, larynx, trachea, bronchus, lung, heart, mediastinum, and pleura.

UT includes cancer of the urinary tract which includes: renal pelvis, ureter, kidney, and bladder.

MC All male cancer which includes: prostate, penis and testis

FC includes all female cancer which includes: female breast, vulva, vagina, cervix uteri, corpus uteri, endometrial, uterus, ovary

[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 anatomical 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