Original Article

Lower Rates of Cancer and All-Cause Mortality in an Adventist Cohort Compared With a US Census Population

Gary E. Fraser, MB ChB, PhD [1]; Candace M. Cosgrove, MPH[2]; Andrew D. Mashchak, MS[1]; Michael J. Orlich, MD, PhD[1]; and Sean F. Altekruse, PhD[3]

BACKGROUND: Previous research suggests that Adventists, who often follow vegetarian diets, live longer and have lower risks for many cancers than others, but there are no national data and little published comparative data for black subjects. **METHODS:** This study compared all-cause mortality and cancer incidence between the nationally inclusive Adventist Health Study 2 (AHS-2) and nonsmokers in US Census populations: the National Longitudinal Mortality Study (NLMS) and its Surveillance, Epidemiology, and End Results substudy. Analyses used proportional hazards regression adjusting for age, sex, race, cigarette smoking history, and education. **RESULTS:** All-cause mortality and all-cancer incidence in the black AHS-2 population were significantly lower than those for the black NLMS populations (hazard ratio [HR] for mortality, 0.64; 95% confidence interval [CI], 0.59-0.69; HR for incidence, 0.78; 95% CI, 0.68-0.88). When races were combined, estimated all-cause mortality was also significantly lower in the AHS-2 population at the age of 65 years (HR, 0.67; 95% CI, 0.64-0.69) and at the age of 85 years (HR, 0.78; 95% CI, 0.75-0.81), as was cancer mortality; this was also true for the rate of all incident cancers combined (HR, 0.70; 95% CI, 0.67-0.74) and the rates of breast, colorectal, and lung cancers. Survival curves confirmed the mortality results and showed that among males, AHS-2 blacks survived longer than white US subjects. **CONCLUSIONS:** Substantially lower rates of all-cause mortality and cancer incidence among Adventists have implications for the effects of lifestyle and perhaps particularly diet on the etiology of these health problems. Trends similar to those seen in the combined population are also found in comparisons of black AHS-2 and NLMS subjects. ***Cancer* 2019;0:1-10**. *© 2019 American Cancer Society*.

KEYWORDS: blacks, cancer, cohort study, mortality, Seventh-Day Adventists.

INTRODUCTION

The Adventist Health Study 2 (AHS-2) began in 2002 with the goal of investigating effects of diet and other lifestyle factors on the risk of cancer among North American Seventh-Day Adventists. Adventists are a health-oriented population and are nearly all nonsmokers. The great majority of Adventists do not drink alcohol, and many avoid caffeine-containing beverages. Adventists have diverse dietary habits. A small percentage are vegans. Many follow a lacto-ovo-vegetarian diet. Approximately half choose omnivorous diets that are often relatively low in meat consumption.[1]

Previous research has suggested that Seventh-Day Adventists have lower risks for many cancers, cardiovascular disease, and diabetes[2] and, in California, live longer (females by 4.4 years and males by 7.3 years) than the general population.[3] Studies have demonstrated the advantage of a vegetarian diet among Adventists. Meat consumption in Adventists

Corresponding author: Gary E. Fraser, MB ChB, PhD, Adventist Health Studies, School of Public Health, Loma Linda University, 24951 N Circle Dr, NH 2033, Loma Linda, CA 92350; gfraser@llu.edu

[1]Center for Nutrition, Healthy Lifestyle and Disease Prevention, School of Public Health, Loma Linda University, Loma Linda, California; [2]US Census Bureau, Washington, DC; [3]Prevention and Population Sciences Program, Division of Cardiovascular Sciences, National Heart Lung and Blood Institute, Bethesda, Maryland

This article is released to inform interested parties of research and to encourage discussion. Any views expressed on statistical, methodological, technical, or operational issues are those of the authors and not necessarily those of the US Census Bureau. These results have been reviewed by the US Census Bureau's disclosure review board (DRB) to ensure that no confidential information is disclosed. The DRB release numbers are CBDRB-FY19-355, CBDRB-FY19-426, CBDRB-FY19-441, CBDRB-FY19-388, and CBDRB-FY19-305.

We gratefully acknowledge the cancer incidence data that were provided via matching with the Alabama State Cancer Registry, the Alaska Cancer Registry, the Arizona Cancer Registry, the Arkansas Cancer Registry, the California Cancer Registry, the Colorado Cancer Registry, the Connecticut Tumor Registry, the District of Columbia Cancer Registry, the Delaware Cancer Registry, the Florida Cancer Data System, the Georgia Department of Public Health, the Hawaii Tumor Registry, the Cancer Data Registry of Idaho (National Cancer Institute contract HHSN261201800006I), the Illinois State Cancer Registry, the Indiana State Cancer Registry, the Iowa Cancer Registry, the Kansas Cancer Registry, the Kentucky Cancer Registry, the Louisiana Tumor Registry, the Maryland Cancer Registry, the Massachusetts Cancer Registry, the Michigan Cancer Surveillance System, the Minnesota Cancer Surveillance System, the Mississippi Cancer Registry, the Missouri Cancer Registry and Research Center, the Montana Central Tumor Registry, the Nebraska Cancer Registry, the Nevada Central Cancer Registry, the New Hampshire State Cancer Registry, the New Jersey State Cancer Registry, the New Mexico Tumor Registry, the New York State Cancer Registry, the North Carolina Central Cancer Registry, the North Dakota Statewide Cancer Registry, the Cancer Data Registry of Ohio, the Oklahoma Central Cancer Registry, the Oregon State Cancer Registry, the Pennsylvania Cancer Registry, the Rhode Island Cancer Registry, the South Carolina Cancer Registry, the South Dakota Cancer Registry, the Tennessee Cancer Registry, the Texas Cancer Registry, the Utah Cancer Registry (National Cancer Institute contract HHSN261201300071), the Vermont Cancer Registry, the Virginia Cancer Registry, the Washington State Cancer Registry, the West Virginia Cancer Registry, the Wisconsin Cancer Reporting System, and the Wyoming Cancer Surveillance Program. We also gratefully acknowledge the review of this work and helpful suggestions made by Dr Eric Feuer, National Cancer Institute, National Institutes of Health.

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.32571, **Received:** February 15, 2019; **Revised:** August 15, 2019; **Accepted:** September 18, 2019, **Published online** Month 00, 2019 in Wiley Online Library (wileyonlinelibrary.com)

has been associated with an increased risk of colon cancer[4] and cardiovascular disease.[5,6] Findings from AHS-2 show that vegetarian Adventists have lower body mass indices; lower prevalences of metabolic syndrome, diabetes, and hypertension; lower all-cause mortality[7]; and, in some instances, a lower risk of cancer in comparison with non-vegetarian Adventists.[8]

These analyses provide the first comparisons of disease rates between a national sample of American Adventists and a comparable sample of the general population. Previous results vary by cancer type, with little published data for black subjects, who are a prominent minority group in both studies. This report compares all-cause mortality rates between AHS-2 and the National Longitudinal Mortality Study (NLMS) and cancer incidence rates between AHS-2 and the Surveillance, Epidemiology, and End Results (SEER) substudy of the NLMS (labeled SEER-NLMS).[9] We adjusted for age, race, sex, education, smoking history (including years quit among former smokers), and location of residence. Given low rates of smoking among Adventists and the well-established risk of death for smoking and certain cancers, we sought a non-Adventist population with information on smoking history to make comparisons independent of smoking history.

MATERIALS AND METHODS

Study Populations and Record Linkages

Details of the AHS-2 cohort, including enrollment methods, have been previously published.[1] This national cohort of Seventh-Day Adventists older than 30 years is approximately 60% female and 26% black. AHS-2 subjects were enrolled from across the United States between 2002 and 2007, and the results here include events during a follow-up period averaging 7.8 years. Subjects completed an extensive lifestyle, medical history, and demographic questionnaire at their enrollment. The NLMS is a mortality follow-up study consisting of cohorts from the US Census Bureau's Current Population Survey (CPS) March Social and Economic Supplement, a complex, national probability sample of households designed to obtain demographic and socioeconomic information. The SEER-NLMS study links CPS survey data to SEER cancer incidence information from SEER 18 registries (excluding Alaska). SEER-NLMS data are restricted to residents of counties within this registry catchment, which accounts for 30% of the US population, including California, Connecticut, Georgia, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, Utah, and metropolitan Detroit and Seattle. To match the AHS-2 population, NLMS and SEER-NLMS respondents were restricted to non-Hispanic whites or non-Hispanic blacks aged 25 years or older who had completed the CPS Tobacco Use Supplement and were either never or former cigarette smokers. For NLMS, a former smoker was someone who had smoked at least 100 cigarettes in his or her lifetime and had quit smoking at least 1 year before the Tobacco Use Supplement survey was completed. Current smokers were excluded from both study data sets because they constituted approximately 1% of the AHS-2 population. Further details of the harmonization of covariates between the 2 studies can be found in the supporting information.

Harmonizing Calendar Times of Follow-Up and Weighting to Adjust for Sampling Differences

To approximate the follow-up time period of the AHS-2 population, NLMS and SEER-NLMS respondents were restricted to those alive without a SEER first primary cancer diagnosis on January 1, 2002. Mortality data from respondents to the NLMS tobacco questionnaire[9] and AHS-2 study members were compared. Incident cancers in the SEER-NLMS and AHS-2 data sets were also compared. Linkage of SEER and NLMS data[9-11] was managed by the US Census Bureau. For AHS-2, start dates (and corresponding ages) were those at entry to the study between 2002 and 2007. Subjects in these study populations were followed through 2011 for new cancer diagnoses.

Individual responses in the NLMS cohort were weighted on the basis of race, ethnicity, and state of residence to represent the noninstitutional US population at the time of the survey. When multiple NLMS subcohorts were combined, the data were reweighted to reflect the whole population. Weighting methods are described in US Census Bureau Technical Papers 40 and 63.[12] The AHS-2 and SEER-NLMS/NLMS data were combined to create a pooled data set of weighted NLMS respondents and unweighted AHS-2 respondents.

Outcome Data

All-cause mortality, incidence of all cancers, and incidence of selected cancer sites were outcomes of interest. The National Death Index was used to obtain mortality data for both studies.

To find incident cancers in the AHS-2 cohort, personal identifiers were linked with US and Canadian cancer registry data via computer-assisted record linkage. Linkages were achieved for 49 states and Washington, DC, but not for Maine. Linkages were approved by human subject committees of participating

registries. In addition to registry linkages, mailed biennial follow-up questionnaires in AHS-2 found additional data on new cancer diagnoses. When participants reported a new cancer that was not found by the registry linkage, further telephone follow-up was performed to clarify possible diagnoses. When a cancer diagnosis was suspected, medical records were requested and reviewed by the principal investigator. In the NLMS study, cancer diagnoses were ascertained by the SEER registries with data from reporting sources on the primary tumor site and clinical characteristics.[13]

Topographic codes from *International Classification of Diseases for Oncology, Third Edition,* were used to define these primary cancer sites: breast (C50.0-C50.9), prostate (C61), endometrial (C54.0-C54.9), pancreatic (C25.0-C25.9), lung (C34.0-C34.9), colon (C18.0-C18.9 but not C18.1), and rectal (C19.9 or C20.9). Carcinomas in situ were not counted as endpoints, and these subjects remained uncensored and at risk for invasive cancers of interest. People with poorly defined and other selected histologic diagnoses were censored at the time of the event: 9050 to 9055, 9140, and 9590 to 9992 (mesothelioma, Kaposi sarcoma, and hematopoietic cancers, respectively).

Covariate Data

We included self-reported data harmonized between the 2 studies from the CPS (NLMS) or the baseline questionnaire (AHS-2) for race (black or white), smoking status (former or never smoker), sex (female or male), education (elementary school, some high school, high school diploma, some college, bachelor's degree, master's degree, or doctoral degree), and geography (residence in a SEER or non-SEER area for the incident cancer; 8 geographical regions for all-cause mortality; details in the supporting information). For former smokers, a time-since-quitting variable was created. In regression models, a variable consisting of the product between this variable and a yes/no former smoker variable was included.

Statistical Analyses

The exposure variable of interest was an indicator variable ("study"), where a value of 1 denoted membership in the AHS-2 population and 0 denoted membership in the NLMS population. Analyses were conducted with the PHREG procedure (SAS version 9.4).[14] Attained age was the time variable, and left truncation removed ages before enrollment into the study.[15,16] Likelihood ratio chi-square statistics were used to test differences between the AHS-2 and NLMS or SEER-NLMS populations. Weighted Cox proportional hazards regression models and their β coefficients and standard errors were used to calculate hazard ratios (HRs) with 95% confidence limits. Empirical survival curves were produced via the PHREG procedure with nominated mean values for most covariates, but proportions of the population living in particular regions (from census data) were used as values for indicator variables representing the geographic region. Because long tails in the original survival curves at ages older than 100 years, particularly for the NLMS study in black females, probably resulted from missed national death index matches, curves were truncated at the age of 90 years. This problem was eliminated in AHS-2 by follow-up with subjects or informers.

Log-log plots were examined to verify proportional hazards assumptions in all models for all variables. For main exposures comparing the 2 studies, there was an appearance of nonproportionality across age ranges for all subjects in analyses of all-cause mortality and other (noncancer) causes of mortality as well as pancreatic cancer incidence. The product term between age and study for the Cox pancreatic cancer model was far from statistical significance and was not retained. Product terms between age and several covariates that were revealed by the plots to violate the proportional hazards assumption were retained in final models. Effect modification between the study variable and covariates was explored for each endpoint. No significant or influential product terms corresponding to these interactions were identified.

Separate analyses were conducted for whites and blacks combined and for blacks separately. Reference categories for categorical covariates were white race, never smoker, female sex, master's/doctoral degree, and the South Atlantic region of residence (mortality analyses).

A variable labeled "SEER" had a value of 1.0 assigned to all SEER-NLMS subjects and AHS-2 subjects who resided in SEER registry areas; otherwise, the value was 0. For the 3.7% of AHS-2 subjects who changed residence, it was possible to estimate the fraction of follow-up time lived in a SEER area, and this fraction was then used as the value for SEER. In regression analyses, the model included this information as 1 – SEER and adjusted for confounding by area of residence. When the 1 – SEER variable took a value of 0, the main effect variable, "study," represented the effect of membership in AHS-2, but living in a SEER area; then those AHS-2 subjects residing in non-SEER areas had an adjustment for that place of residence.

To evaluate a healthy volunteer effect in the AHS-2 cohort, we performed analyses for all-cause mortality and all cancer incidence and removed person-years in the

TABLE 1. Characteristics of the NLMS and AHS-2 Populations

	All-Cause Mortality Study		Cancer Incidence Study	
	NLMS	AHS-2	SEER-NLMS	AHS-2
Total subjects, No.	383,600	86,610	62,074	79,641
Race, No. (%)				
White	340,000 (89)	63,370 (73)	55,170 (89)	57,165 (72)
Black	43,560 (11)	23,240 (27)	6906 (11)	22,476 (28)
Sex, No. (%)				
Male	173,800 (45)	30,200 (35)	28,510 (46)	27,719 (35)
Female	209,800 (55)	56,410 (65)	33,570 (54)	51,922 (65)
Smoking, No. (%)				
Former smokers	114,500 (30)	16,490 (19)	17,860 (29)	14,941 (19)
Never smokers	269,100 (70)	70,120 (81)	44,210 (71)	64,700 (81)
Age, No. (%)				
<50 y	181,200 (47)	27,468 (31)	32,540 (52)	26,659 (33)
50-59 y	75,890 (20)	20,710 (24)	12,420 (20)	19,542 (25)
60-69 y	54,530 (14)	17,584 (21)	7822 (13)	15,897 (20)
70-79 y	43,840 (12)	13,968 (16)	5746 (9)	11,844 (15)
≥80 y	28,090 (7)	6883 (8)	3552 (6)	5699 (7)
Education, No. (%)				
Elementary school	16,470 (4)	2267 (3)	1887 (3)	1998 (3)
Some high school	30,410 (8)	4739 (5)	3727 (6)	4248 (5)
High school diploma	123,800 (32)	16,111 (19)	17,390 (28)	14,427 (18)
Some college	97,330 (25)	29,601 (34)	17,250 (28)	26,916 (34)
Bachelor's degree	75,300 (20)	18,261 (21)	14,000 (23)	16,771 (21)
Master's or doctoral degree	40,310 (11)	15,631 (18)	7709 (12)	14,197 (18)
Deaths, No. (%)	35,230 (9)	7250 (8)		

Abbreviations: AHS-2, Adventist Health Study 2; NLMS, National Longitudinal Mortality Study; SEER, Surveillance, Epidemiology, and End Results.
NLMS study data are reported, as received, to an accuracy of 4 significant digits. The disclosure review board approval number is CBDRB-FY19-305.

AHS-2 cohort within the first 2 years after enrollment into the study.[3,17] All computer analyses were conducted at the U.S. Census Bureau office, Washington DC, by one of us (CMC) in consultation with Loma Linda investigators (GEF and ADM).

RESULTS

The baseline characteristics of the study populations are shown in Table 1, and characteristics according to race are shown in Table 2. Among 470,210 subjects with vital status data (383,600 from the NLMS and 86,610 from the AHS-2), there were 35,230 deaths in NLMS and 7250 deaths in AHS-2. In comparison with AHS-2, there were a higher percentage of white participants (89% vs 73%), more males (45% vs 35%), and younger subjects (47% under the age of 50 years vs 31%) in the NLMS population. The percentage of past smokers was also higher in the NLMS population (30% vs 19%). There were more white former smokers in NLMS (31% vs 17%), whereas in AHS-2, the proportion was 19% in both racial groups. Blacks were comparatively younger in both studies and were less well educated in NLMS. The AHS-2 subjects were overall better educated. There were large differences in region of residence between the races and between the 2 studies.

There were 62,074 SEER-NLMS respondents and 79,641 AHS-2 respondents in the database used for analyses of incident cancers; 3927 SEER-NLMS respondents (6.3%) experienced an invasive cancer diagnosis, as did 4735 of the AHS-2 respondents (5.9%).

Comparison of Incident Cancers in the AHS-2 and SEER-NLMS Populations: All Subjects

A comparison of incidence rates of common cancers (breast, prostate, and colorectal) and medium-frequency cancers (rectal, endometrial, lung, and pancreatic) between the AHS-2 and SEER-NLMS populations is shown in Figure 1. The AHS-2 population had significantly lower rates of all incident cancers (HR, 0.70; $P < .0001$) and specifically cancers of the breast (HR, 0.70; $P < .0001$), colorectum (HR, 0.84; $P = .035$), rectum (HR, 0.50; $P < .0001$), and lungs (HR, 0.70; $P = .002$).

Comparison of Incident Cancer Rates Between the Black AHS-2 and SEER-NLMS Populations

Comparisons of rates of all incident cancers and several common incident cancers between the black AHS-2 and SEER-NLMS populations are also shown in Figure 1. The incidence of all cancers was lower in the black AHS-2 population (HR, 0.78; $P < .0002$).

TABLE 2. Characteristics of the Black and White Subpopulations of the SEER-NLMS, NLMS, and AHS-2 Cohorts

	NLMS		AHS-2	
	Black	White	Black	White
Total subjects, No.	43,560	340,000	23,240	63,370
Sex, No. (%)				
Male	17,200 (46)	156,600 (46)	6890 (30)	23,310 (37)
Female	26,360 (54)	183,400 (54)	16,350 (70)	40,060 (63)
Smoking, No. (%)				
Former smokers	7533 (17)	106,900 (31)	4483 (19)	12,010 (19)
Never smokers	36,030 (83)	233,100 (69)	18,760 (81)	51,360 (81)
Age, No. (%)				
<50 y	25,580 (59)	155,700 (45)	10,080 (43)	17,390 (28)
50-59 y	7507 (17)	68,390 (20)	5962 (26)	14,750 (23)
60-69 y	5136 (12)	49,390 (15)	3996 (17)	13,590 (21)
70-79 y	3460 (8)	40,380 (12)	2390 (10)	11,580 (18)
≥80 y	1882 (4)	26,210 (8)	817 (4)	6066 (10)
Education, No. (%)				
Elementary school	3058 (7)	13,410 (4)	1192 (5)	1075 (2)
Some high school	6446 (15)	23,960 (7)	1669 (7)	3070 (5)
High school diploma	14,880 (34)	108,900 (32)	4141 (18)	11,970 (19)
Some college	11,560 (27)	85,770 (25)	7989 (34)	21,610 (34)
Bachelor's degree	5174 (12)	70,130 (21)	4280 (19)	13,980 (22)
Master's or doctoral degree	2446 (6)	37,860 (11)	3972 (17)	11,660 (18)
Region, No. (%)				
New England	866 (2)	21,200 (6)	481 (2)	1438 (2)
Mid-Atlantic	6224 (14)	50,480 (15)	4266 (19)	2495 (4)
East North Central	6365 (15)	61,580 (18)	2646 (11)	6888 (11)
West North Central	1262 (3)	29,750 (9)	723 (3)	4288 (7)
South Atlantic	15,030 (34)	58,940 (17)	8194 (35)	8927 (14)
East South Central	4734 (11)	21,240 (6)	2076 (9)	4577 (7)
West South Central	5488 (13)	30,640 (9)	1875 (8)	3946 (6)
Mountain	614 (1)	21,830 (7)	448 (2)	6089 (10)
Pacific	2973 (7)	44,370 (13)	2534 (11)	24,720 (39)
Deaths, No.	3324	31,900	1282	5968
	SEER-NLMS		AHS-2	
	Black	White	Black	White
Incident cancers, No. (%)[a]				
All cancers	371	3556	1104	3631
Breast	58 (16)	540 (15)	224 (20)	668 (18)
Prostate	75 (20)	553 (16)	299 (27)	762 (21)
Colon	26 (7)	222 (6)	89 (8)	288 (8)
Rectum	11 (3)	99 (3)	24 (2)	75 (2)
Lung	38 (10)	249 (7)	61 (6)	174 (5)
Pancreas	13 (4)	91 (3)	24 (2)	115 (3)
Endometrium	9 (2)	117 (3)	51 (5)	187 (5)

Abbreviations: AHS-2, Adventist Health Study 2; NLMS, National Longitudinal Mortality Study; SEER, Surveillance, Epidemiology, and End Results.
NLMS study data are reported, as received, to an accuracy of 4 significant digits. The disclosure review board approval number is CBDRB-FY19-305.
[a]For cancers, the values in parentheses are the percentages of all cancers.

Sensitivity Analyses for Cancer Incidence

In analyses designed to evaluate the adequacy of adjustments for past smoking, we calculated HRs among never smokers only for total and lung cancers. The resulting HR for lung cancer was closer to the null and no longer statistically significant (HR, 0.74; 95% confidence interval [CI], 0.53-1.03; $P = .076$). However, for the incidence of all cancers, the HR remained significant among never smokers (HR for all subjects, 0.71; 95% CI, 0.67-0.76; $P < .0001$; HR for black subjects, 0.75; 95% CI, 0.65-0.88; $P = .0003$). These associations persisted after the removal of person-years in the AHS-2 cohort within the first 2 years of study enrollment (HR for the whole cohort, 0.71; 95% CI, 0.67-0.75; $P < .0001$; HR for the black cohort, 0.80; 95% CI, 0.68-0.93; $P < .004$) as a means of decreasing any healthy volunteer bias.

All-Cause, Cancer, and Other Mortality

All-cause mortality was significantly lower in the AHS-2 population than the NLMS population but

Cancer Type	Subgroup	HR (95% CI)	*P* value
All Cancer	All	0.70 (0.67-0.74)	<.0001
	Black	0.78 (0.68-0.88)	.0002
Breast	All	0.70 (0.62-0.79)	<.0001
	Black	0.83 (0.60-1.15)	.26
Prostate	All	0.91 (0.81-1.03)	.12
	Black	1.11 (0.84-1.47)	.47
Colorectal	All	0.84 (0.71-0.99)	.04
	Black	0.68 (0.46-1.02)	.057
Colon	All	1.01 (0.84-1.22)	.96
Rectal	All	0.50 (0.36-0.69)	<.0001
Endometrial	All	0.91 (0.71-1.16)	.45
Lung	All	0.70 (0.56-0.88)	.002
Pancreatic	All	0.93 (0.70-1.23)	.61

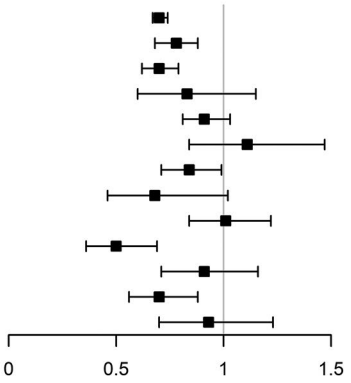

Figure 1. Incidence of all, common, and medium-frequency cancers: HRs comparing rates in the Adventist Health Study 2 and the National Longitudinal Mortality Study SEER substudy for total and black populations. Adjustments have been made for sex, smoking, education, and region of residence (SEER vs non-SEER areas). Listed *P* values come from chi-square tests of the null hypothesis that HR equals 1. CI indicates confidence interval; HR, hazard ratio; SEER, Surveillance, Epidemiology, and End Results.

Mortality	Subgroup	HR (95% CI)	*P* value
All-cause	All (age 65)*	0.67 (0.64-0.69)	<.0001
	All (age 85)*	0.78 (0.75-0.81)	<.0001
	Blacks	0.64 (0.59-0.69)	<.0001
Cancer	All	0.90 (0.85-0.95)	<.0001
	Blacks	0.83 (0.73-0.95)	.0007
Other	All (age 65)*	0.60 (0.57-0.62)	<.0001
	All (age 85)*	0.72 (0.65-0.80)	<.0001
	Blacks	0.58 (0.54-0.64)	<.0001

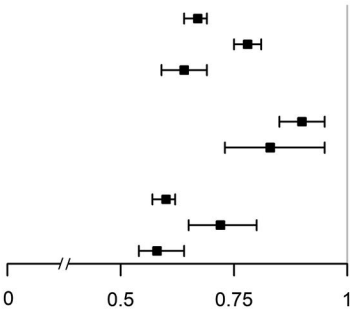

Figure 2. All-cause, cancer, and other mortality: HRs comparing mortality in the Adventist Health Study 2 and the National Longitudinal Mortality Study for total and black populations. Adjustments have been made for sex, smoking, education, and region of residence. Listed *P* values come from chi-square tests of the null hypothesis that HR equals 1. *The comparisons between the Adventist Health Study 2 and the National Longitudinal Mortality Study here depend on age. Two ages have been selected to illustrate these differences. CI indicates confidence interval; HR, hazard ratio.

varied with age (model-estimated HR at the age of 65 years, 0.67; $P < .0001$; estimated HR at the age of 85 years, 0.78; $P < .0001$; Fig. 2). All-cause mortality in the black AHS-2 population, in comparison with the black NLMS population, was also significantly lower (HR, 0.64; $P < .0001$) without a significant age dependence. Cancer mortality was also lower in the total (HR, 0.90; $P < .0001$) and black populations (HR, 0.83; $P = .0007$), although less so in comparison with other causes of mortality (HR for total population aged 65 years, 0.60; $P < .0001$; HR for total population aged 85 years, 0.72; $P < .0001$; HR for blacks, 0.58; $P < .0001$).

We further explored this by estimating multivariate-adjusted survival curves, as shown in Figures 3 and 4, which confirmed better survival among Adventists of both racial groups. Interestingly, black Adventist males had better survival than white census males ($P < .001$). In both studies, whites had better overall survival than black subjects.

Sensitivity Analyses for All-Cause Mortality

In sensitivity analyses, all-cause mortality remained significantly lower in the AHS-2 population among never smokers only (HR for all subject analyses, 0.75; 95% CI, 0.72-0.77; $P < .0001$; HR for black subjects, 0.65; 95% CI, 0.60-0.71; $P < .0001$) and after the removal of AHS-2 person-years within the first 2 years after enrollment (estimated HR for all subject analyses at the age of 65 years, 0.73; 95% CI, 0.70-0.76; $P < .0001$; estimated

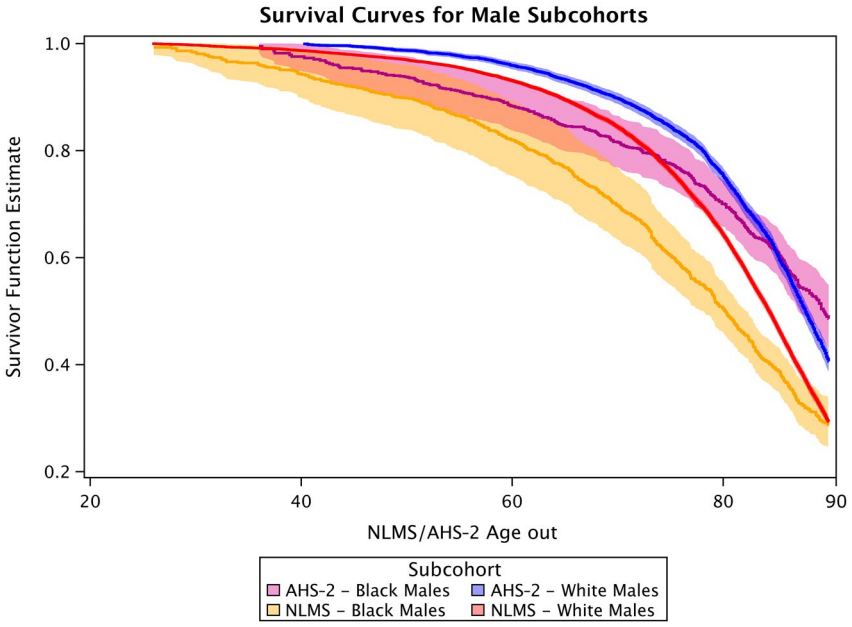

Figure 3. Comparative survival curves for black and white AHS-2 and NLMS male study subjects. The covariate values chosen for calculating these curves were as follows: high school/trade school graduate for education; nonsmoking; and 0.177 for New England/Middle Atlantic, 0.148 for East North Central, 0.066 for West North Central, 0.195 for South Atlantic, 0.059 for East South Central, 0.120 for West South Central, 0.072 for Mountain, and 0.163 for Pacific (regions). AHS-2 indicates Adventist Health Study 2; NLMS, National Longitudinal Mortality Study.

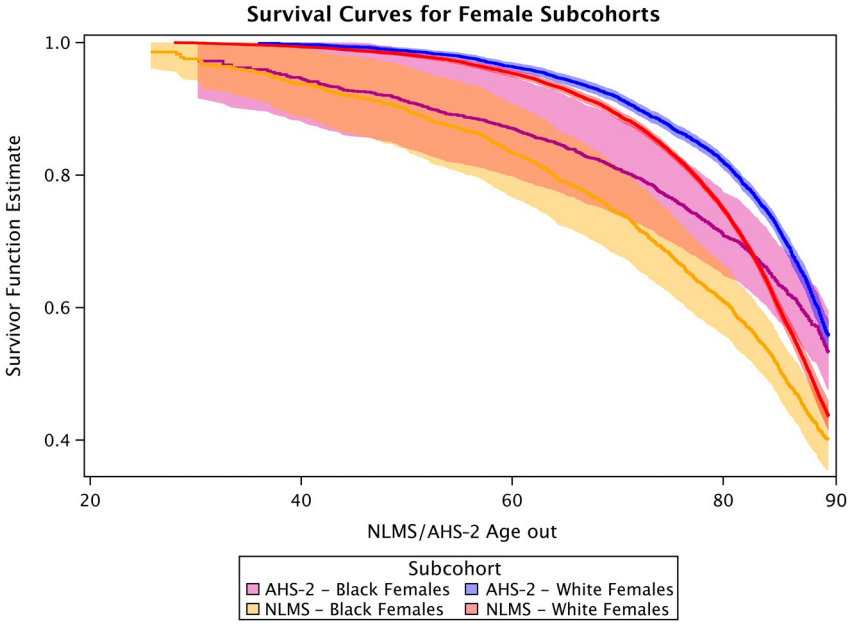

Figure 4. Comparative survival curves for black and white AHS-2 and NLMS female study subjects. The covariate values chosen for calculating these curves were as follows: high school/trade school graduate for education; nonsmoking; and 0.177 for New England/Middle Atlantic, 0.148 for East North Central, 0.066 for West North Central, 0.195 for South Atlantic, 0.059 for East South Central, 0.120 for West South Central, 0.072 for Mountain, and 0.163 for Pacific (regions). AHS-2 indicates Adventist Health Study 2; NLMS, National Longitudinal Mortality Study.

HR for all subject analyses at the age of 85 years, 0.90; 95% CI, 0.87-0.94; $P < .0001$; HR for black subjects, 0.71; 95% CI, 0.66-0.77; $P < .0001$).

DISCUSSION

This study for the first time directly compares all-cause mortality and cancer incidence rates between a national Seventh-Day Adventist study population and a study population that represents the general population of the United States while adjusting for education, past smoking habits, age, region of residence, sex, and race (as appropriate). A caveat is that the census population for incident cancer comparisons is restricted to SEER states, with an adjustment for this being made within the AHS-2 population. The principal findings from these comparisons are the significantly lower rates of all-cause mortality and incidence of all cancers combined in the AHS-2 population (by 33% and 30%, respectively) and the lower incidence rates specifically for breast, colorectal, rectal, and lung cancers (by 30%, 16%, 50%, and 30%, respectively). All-cause mortality and the incidence of all cancers combined were also significantly lower in the black AHS-2 population than the black NLMS population (by 36% and 22%, respectively). Cancer mortality was less impressively lower in comparison with other causes of mortality. Survival curves show that particularly premature deaths appear to be prevented among Adventists.

These results are consistent with and extend previous research showing longer life expectancy and lower risks for most cancers among Seventh-Day Adventists in comparison with the general population in California and in other countries.[2,18-20] It has previously been shown that Californian Seventh-Day Adventists have a greater life expectancy than other Californians by 7.3 years (males) and by 4.4 years (females).[3] Lifestyle choices are a likely explanation as these contrasts increase when the Adventists are restricted to vegetarians. A crossover phenomenon in which blacks have lower mortality than whites at older ages is well described.[21,22] We see some hint of this by the age of 90 years in the survival curves. Significantly, quality-of-life comparisons between AHS-2 and the general population find similar advantages for white and black Adventists,[23] and this suggests that Adventists may enjoy relatively good health during their additional years of survival. The fact that cancer mortality HRs are less reduced in Adventists than cancer incidence rates may suggest that cancers particularly affected in Adventists may be at sites less likely to be fatal or that in many sites they are the less aggressive variants. Other explanations are possible and deserve further exploration.

Colon cancer and perhaps prostate cancer look to be outliers in the cancer results, with the HRs closer to 1.0 in the total population and to 1.11 for prostate cancer among black men. These may reflect a true lack of difference in the occurrence of these cancers between Adventists and others, but for prostate cancer, a diagnostic bias is also possible. Higher rates may be found because of earlier diagnosis in the relatively well-educated Adventist population, where there is an emphasis on prevention. Despite adjustments for education, the effects of more frequent prostate cancer screening, especially among relatively well-educated black Adventists,[24,25] may be present. Because higher dairy consumption has been associated with lower rates of colorectal cancers in this population,[26] we speculate that the lower dairy intake among vegetarian Adventists[27] may partially offset the acknowledged benefits[28] of their lower red meat consumption. With the relatively small numbers of rectal cancers, the unexpected difference between colon and rectal cancer results in our analyses may be due to chance.

Life expectancy in the United States is determined mainly by mortality from chronic diseases, especially cardiovascular disease, cancers, obesity, and diabetes.[29,30] An estimated 55% to 60% of deaths are attributed to cigarette smoking, overweight, physical inactivity, and poor diet.[30,31] Seventh-Day Adventists have greater adherence than usual to healthier lifestyle habits. Nonsmoking, regular physical activity, avoidance of overweight and obesity,[3,32] and a healthy diet are important cornerstones of the Adventist lifestyle. Meat consumption is relatively low, with many adopting a vegetarian diet.[1] Vegetarian Adventists, even in comparison with the relatively low-meat-eating Adventist nonvegetarians, have reduced all-cause mortality,[7,33] hypertension, and diabetes and a lower incidence of all cancers and gastrointestinal system cancers. Mechanisms responsible for these health effects may be related to adverse effects of meat consumption[34-36] and protective effects of dietary phytochemicals in the fruits, vegetables, nuts, and legumes consumed by vegetarians to replace animal products. These topics are discussed in detail elsewhere.[37,38] Social and religious factors that result in greater social support, community involvement, and access to material and psychological help may also differ between Adventists and others.[39] These factors can reduce stress and provide options for assistance that may also affect mortality.[40,41] There is less evidence that they would affect cancer incidence.

The lower all-cause mortality and incidence of all cancers observed among black subjects in the AHS-2 in comparison with the black US population is of interest. Black US men and women have a shorter overall life expectancy than their white counterparts (by 5.4 and 3.8 years, respectively).[42] Our findings suggest that the adoption of healthy lifestyles at the population level could lengthen life expectancy in this racial group.

The study has several strengths. Both populations were diverse in terms of age, sex, race, geography, occupation, and education. Self-selection for Adventists with more healthy lifestyles was possible, but this should not have biased β coefficients, which are indirect tests of the hypothesis that health habits, especially diet, are determinants of life expectancy and risks of certain cancers. When evaluating survival curves, we explored the effect of removing the first years of follow-up on estimated life expectancy. A mild reduction in estimates was seen (always less than 1 year), and this indicated that the "acute" healthy volunteer effect had a small (but measurable) impact on results.

Despite appropriate adjustments, residual confounding remains possible. A smaller study effect (comparison of the cohorts) was seen for lung cancer incidence in analyses restricted to never smokers, possibly because of some misclassification of past smoking. Because of small numbers of cases among never smokers, the study effect in this analysis had wide CIs that overlapped with those of the full analysis. Thus, differences between these 2 results could also be explained by chance. Residual confounding from past smoking was unlikely to have affected other outcomes as strongly as lung cancer when analyses were restricted to never smokers. The power for analyses of specific cancers was also limited in the black population.

In conclusion, our study directly compares a national (US) Seventh-Day Adventist population with a representative sample of the US population, and it controls for education and smoking. Significantly lower rates of all-cause mortality were seen in the AHS-2 population along with lower incidences of all cancers combined and breast, colorectal, rectal, and lung cancers. All-cause mortality and the incidence of all cancers combined were also significantly lower in the black AHS-2 population than the black NLMS population. Notably, the AHS-2 black males had better survival than the white NLMS males. These results invite speculation that observed survival and mortality differences may be due to lifestyle choices and conferrable to general white and black populations if they were to adopt healthy lifestyles.

FUNDING SUPPORT

The Adventist Health Study 2 was supported by the National Cancer Institute (grant 1UO1CA152939) and the World Cancer Research Fund (UK) (grant 2009/93). The National Longitudinal Mortality Study was supported by interagency funding from the National Institutes of Health, the Centers for Disease Control and Prevention, and the US Census Bureau.

CONFLICT OF INTEREST DISCLOSURES

Gary E. Fraser, Andrew D. Mashchak and Michael J. Orlich report being members of the Seventh-day Adventist church, and Michael J. Orlich and Gary E. Fraser are employees of Loma Linda University Health's Faculty Medical Group; Loma Linda University Health is a Seventh-Day Adventist institution. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Gary E. Fraser: Responsibility for the overall content (guarantor), conceptualization, funding acquisition, methodology, administration, and writing–original draft. **Candace M. Cosgrove:** Formal analysis. **Andrew D. Mashchak:** Formal analysis and methodology. **Michael J. Orlich:** Writing–review and editing and project administration. **Sean F. Altekruse:** Administration, formal analysis, and writing–review and editing.

REFERENCES

1. Butler TL, Fraser GE, Beeson WL, et al. Cohort profile: the Adventist Health Study-2 (AHS-2). *Int J Epidemiol*. 2008;37:260-265.
2. Fraser GE. Diet, Life Expectancy, and Chronic Disease: Studies of Seventh-Day Adventists and Other Vegetarians. New York: Oxford University Press; 2003.
3. Fraser GE, Shavlik DJ. Ten years of life: is it a matter of choice? *Arch Intern Med*. 2001;161:1645-1652.
4. Singh PN, Fraser GE. Dietary risk factors for colon cancer in a low-risk population. *Am J Epidemiol*. 1998;148:761-774.
5. Tharrey M, Mariotti F, Mashchak A, et al. Patterns of plant and animal protein intake are strongly associated with cardiovascular mortality: the Adventist Health Study-2 cohort. *Int J Epidemiol*. 2018;47:1603-1612.
6. Alshahrani SM, Fraser GE, Sabate J, et al. Red and processed meat and mortality in a low meat intake population. *Nutrients*. 2019;11:E622.
7. Orlich MJ, Singh PN, Sabate J, et al. Vegetarian dietary patterns and mortality in Adventist Health Study 2. *JAMA Intern Med*. 2013;173:1230-1238.
8. Orlich MJ, Fraser GE. Vegetarian diets in the Adventist Health Study 2: a review of initial published findings. *Am J Clin Nutr*. 2014;100(suppl 1):353S-358S.
9. National Cancer Institute. National Longitudinal Mortality Study (NLMS) and the Linked SEER-NLMS Database. Accessed October 9, 2019. https://www.census.gov/did/www/nlms/
10. Clegg LX, Reichman ME, Miller BA, et al. Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the Surveillance, Epidemiology, and End Results: National Longitudinal Mortality Study. *Cancer Causes Control*. 2009;20:417-435.
11. Clegg LX, Reichman ME, Hankey BF, et al. Quality of race, Hispanic ethnicity, and immigrant status in population-based cancer registry data: implications for health disparity studies. *Cancer Causes Control*. 2007;18:177-187.
12. US Census Bureau. Technical Papers 40 and 63. Revised March 14, 2016. Accessed April 6, 2016. https://www.census.gov/programs-surveys/cps/technical-documentation/complete.html
13. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Accessed August 30, 2019. http:seer.cancer.gov
14. SAS Institute. SAS System for Unix. Version 9.4. SAS Institute Inc; 2012.
15. Cho H, Mariotto AB, Mann BS, et al. Assessing non–cancer-related health status of US cancer patients: other-cause survival and comorbidity prevalence. *Am J Epidemiol*. 2013;178:339-349.

16. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol*. 1997;145:72-80.
17. Lindsted KD, Fraser GE, Steinkohl M, et al. Healthy volunteer effect in a cohort study: temporal resolution in the Adventist Health Study. *J Clin Epidemiol*. 1996;49:783-790.
18. Jensen OM. Cancer risk among Danish male 7th-Day Adventists and other temperance society members. *J Natl Cancer Inst*. 1983; 70:1011-1014.
19. Fonnebo V. Mortality in Norwegian Seventh-Day Adventists 1962-1986. *J Clin Epidemiol*. 1992;45:157-167.
20. Berkel J, de Waard F. Mortality pattern and life expectancy of Seventh-Day Adventists in the Netherlands. *Int J Epidemiol*. 1983;12:455-459.
21. Manton KG, Poss SS, Wing S. The black/white mortality crossover: investigation from the perspective of the components of aging. *Gerontologist*. 1979;19:291-300.
22. Guralnik JM, Land KC, Blazer D, et al. Educational status and active life expectancy among older blacks and whites. *N Engl J Med*. 1993;329:110-116.
23. Lee JW, Morton KR, Walters J, et al. Cohort profile: the Biopsychosocial Religion and Health Study (BRHS). *Int J Epidemiol*. 2009;38:1470-1478.
24. Ibrayev Y, Oda K, Fraser GE, et al. Utilization of prostate cancer screening according to dietary patterns and other demographic variables. The Adventist Health Study-2. *J Cancer*. 2013;4:416-426.
25. Bockerman P, Maczulskij T. The education–health nexus: fact and fiction. *Soc Sci Med*. 2016;150:112-116.
26. Tantamango-Bartley Y, Knutsen SF, Jaceldo-Siegl K, et al. Independent associations of dairy and calcium intakes with colorectal cancers in the Adventist Health Study-2 cohort. *Public Health Nutr*. 2017; 20:2577-2586.
27. Orlich MJ, Jaceldo-Siegl K, Sabate J, et al. Patterns of food consumption among vegetarians and non-vegetarians. *Br J Nutr*. 2014; 112:1644-1653.
28. Bouvard V, Loomis D, Guyton KZ, et al. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol*. 2015;16:1599-1600.
29. Wong MD, Shapiro MF, Boscardin WJ, et al. Contribution of major diseases to disparities in mortality. *N Engl J Med*. 2002;347:1585-1592.
30. Danaei G, Rimm EB, Oza S, et al. The promise of prevention: the effects of four preventable risk factors on national life expectancy and life expectancy disparities by race and county in the United States. *PLoS Med*. 2010;7:e1000248.
31. van Dam RM, Li T, Spiegelman D, et al. Combined impact of lifestyle factors on mortality: prospective cohort study in US women. *BMJ*. 2008;337:a1440.
32. Fraser GE, Dysinger W, Best C, et al. Ischemic-heart-disease risk-factors in middle-aged 7th-Day-Adventist men and their neighbors. *Am J Epidemiol*. 1987;126:638-646.
33. Fraser GE. Associations between diet and cancer, ischemic heart disease, and all-cause mortality in non-Hispanic white California Seventh-Day Adventists. *Am J Clin Nutr*. 1999;70:532s-538s.
34. Wang X, Lin X, Ouyang YY, et al. Red and processed meat consumption and mortality: dose-response meta-analysis of prospective cohort studies. *Public Health Nutr*. 2016;19:893-905.
35. Friedrich MJ. Processed meat consumption associated with increased cancer risk. *JAMA*. 2015;314:2496-2496.
36. Micha R, Wallace SK, Mozaffarian D. Red and processed meat consumption and risk of incident coronary heart disease, stroke, and diabetes mellitus: a systematic review and meta-analysis. *Circulation*. 2010;121:2271-2283.
37. Ros E, Tapsell LC, Sabate J. Nuts and berries for heart health. *Curr Atheroscler Rep*. 2010;12:397-406.
38. Norat T, Aune D, Chan D, et al. Fruits and vegetables: updating the epidemiologic evidence for the WCRF/AICR lifestyle recommendations for cancer prevention. *Cancer Treat Res*. 2014;159:35-50.
39. Fraser GE, HallerWade TM, Morrow S. Social support in Seventh-Day Adventists and their neighbors. *J Relig Health*. 1997;36:231-239.
40. Ellwardt L, van Tilburg T, Aartsen M, et al. Personal networks and mortality risk in older adults: a twenty-year longitudinal study. *PLoS One*. 2015;10:e0116731.
41. Olaya B, Domenech-Abella J, Moneta MV, et al. All-cause mortality and multimorbidity in older adults: the role of social support and loneliness. *Exp Gerontol*. 2017;99:120-126.
42. Harper S, MacLehose RF, Kaufman JS. Trends in the black-white life expectancy gap among US states, 1990-2009. *Health Aff (Millwood)*. 2014;33:1375-1382.

Lower Rates of Cancer and All-Cause Mortality in an Adventist Cohort Compared With a US Census Population

Gary E. Fraser, Candace M. Cosgrove, Andrew D. Mashchak, Michael J. Orlich, and Sean F. Altekruse

In comparison with a national census population, all-cause and cancer mortality rates and incidence rates for many cancers are substantially lower in a national Seventh-Day Adventist population. This is also true for a comparison of black census subjects and black Adventist subjects.