Cohort Profile: The Adventist Health Study-2 (AHS-2)

Terry L Butler,1* Gary E Fraser,1 W Lawrence Beeson,1 Synnøve F Knutsen,1 R Patti Herring,1 Jacqueline Chan,1 Joan Sabaté,1 Susanne Montgomery,1 Ella Haddad,1 Susan Preston-Martin,2 Hannelore Bennett1 and Karen Jaceldo-Siegl1

How did the study come about?

The Adventist Health Study-2 (AHS-2) began in 2002 with the goal of investigating the role of selected foods to change the risk of cancer. AHS-2 is designed to provide more precise and comprehensive results than previous pioneering research among Seventh-day Adventists,1–6 a unique health oriented population with diverse dietary habits.

The Adventist church, of 24 million adherents worldwide, promotes a healthy lifestyle. Church members are expected to be non-smokers and non-alcohol users, and are encouraged to eat a vegetarian diet. Many also avoid caffeine-containing beverages. However, adherence to these recommendations is quite variable.

Adventists in North America are almost entirely a non-smoking population. The vast majority are non-drinkers and the small number who consume alcohol do so infrequently. But they have a wide diversity in dietary practices. Two previous longitudinal studies in California showed a small percentage are total vegetarians, many follow a lacto-ovo-vegetarian diet or eat meat less than once per week (semi-vegetarian) and about half have omnivorous diets similar to the general population.7

These studies in California, the Adventist Mortality Study (AMS)8,9 from 1960–66 and the first Adventist Health Study (AHS-1)10–13 from 1974–88 indicated that Adventists had lower risks for most cancers, cardiovascular disease and diabetes. Females lived 4.4 years and males 7.3 years longer when compared with the general California population.7,14 These studies also showed the advantage of a vegetarian diet among Adventists, found strong evidence that meat increased risk of colon cancer13 and coronary heart disease,11,12 Other significant associations between cancers and other foods have also been reported.7,16–18

In the USA, it is estimated that there will be 1,444,920 new cases of cancer in 2007 (prostate 218,890, breast 180,510 and colon 112,340).19 It has been suggested that the lower incidence of prostate and breast cancer in the Far East may be due to the frequent consumption of soy.20–23 Adventists, in North America, with high levels and a wide range of soy consumption offer better opportunities than perhaps any other large group with a western diet to investigate the role of soy and other nutrients, such as calcium, in risk of cancers of the breast, prostate and colon.

Thus, various characteristics of Adventists: the diversity in soy consumption and other foods, the virtual elimination of confounding from smoking and alcohol, the findings of previous studies and the potential to include a large group of African-Americans resulted in the National Cancer Institute funding Loma Linda University to undertake AHS-2, with the goal to enroll 100,000 Adventists.

Table 1 provides an overview and compares some characteristics of AHS-2 with the other Seventh-day Adventist cohort studies in California.

What does it cover?

The broad scope of 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.

The primary aims of the currently funded study are to investigate the possible protective role for dietary soy proteins and isoflavones on risk of prostate, breast and colon cancers; to provide further evidence of a possible protective role of vitamin D for these cancers; to further evaluate a possible protective effect of dietary calcium on risk of colon cancer, and a possible hazardous effect on risk of prostate cancer; and to help decide whether dietary linolenic acid increases risk of prostate cancer.
The study will also investigate possible dietary causes for the particularly high incidence of prostate cancer in a population of African-American men, and compare this incidence with that of a Caucasian male population adhering to a broadly similar lifestyle.

Who is in the sample?
The sample includes Seventh-day Adventist church members living in the USA and Canada who are 30 years and older, and who are sufficiently fluent in English to complete the lengthy lifestyle questionnaire. Most participants are either Caucasian or Black/African-American. There are smaller numbers from other ethnic minorities.

There are about one million Adventists in the USA and Canada. Although church membership records do not contain data on age, race and gender, church officials estimate that of those members who regularly attend English language churches and are 30 years or older, approximately 90 000 are Black members and 260 000 are non-Black members (Figure 1).

Enrolment commenced in February 2002 and by May 2007 more than 96 000 participants had completed the lengthy lifestyle questionnaire. Of this number, about 25 500 are Black/African-American and 62 500 are females. There is a wide geographic spread of participants (Figure 2).

The data presented in this article pertains to the 90 156 participants for whom information on the reported variables has been checked and is currently available.

### Enrolment methods
The basic recruitment model targeted the two major English-speaking congregation groups in the Seventh-day Adventist church in the USA and Canada—1000 Black (African-American and Caribbean) congregations and 3500 other congregations (mostly Caucasian, but including some Latino and Asian). For simplicity of designation these two groups of churches are referred to as ‘Black’ and ‘non-Black churches’. Recruitment was church-by-church and staged by geographic region.

Local church pastors selected one or two church members to be the study coordinators and chose a

### Table 1 Characteristics of Seventh-day Adventist cohort studies in the USA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adventist Mortality Study (AMS)</th>
<th>Adventist Health Study-1 (AHS-1)</th>
<th>Adventist Health Study-2 (AHS-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographic region</td>
<td>California</td>
<td>California</td>
<td>50 States and Canada</td>
</tr>
<tr>
<td>Study participants</td>
<td>22 940</td>
<td>34 192</td>
<td>96 194 (as of May 31, 2007)</td>
</tr>
<tr>
<td>Congregations</td>
<td>234</td>
<td>437</td>
<td>4500</td>
</tr>
<tr>
<td>Years of follow-up</td>
<td>1960–76</td>
<td>1976–82</td>
<td>2002 (ongoing)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1976–88 (mortality)</td>
</tr>
<tr>
<td>Outcome of interest</td>
<td>Mortality</td>
<td>Incidence and mortality</td>
<td>Mortality</td>
</tr>
<tr>
<td>Demographics</td>
<td>Female (%) 64.6%</td>
<td>60.1%</td>
<td>65.1%</td>
</tr>
<tr>
<td></td>
<td>Mean age (years) 50.9</td>
<td>54.3</td>
<td>60.2</td>
</tr>
<tr>
<td></td>
<td>Age range (years) 35–90</td>
<td>25–90</td>
<td>30–112</td>
</tr>
<tr>
<td></td>
<td>White (non-Hispanic) (%) 100%</td>
<td>100%</td>
<td>65.3%</td>
</tr>
<tr>
<td></td>
<td>Black (%) 0%</td>
<td>0%</td>
<td>26.9%</td>
</tr>
</tbody>
</table>

The study will also investigate possible dietary causes for the particularly high incidence of prostate cancer in a population of African-American men, and compare this incidence with that of a Caucasian male population adhering to a broadly similar lifestyle.
promotion start date. Information resources (promotional guidelines, brochures, video, posters and announcements) were provided. Each church had a suggested enrolment goal, based on membership, and received weekly progress reports from the research office during the 7–8 weeks of promotion. However, the actual recruitment approach differed between the Black and non-Black churches.

In non-Black churches, we used previously tested promotional and motivational strategies similar to the successful AHS-1 recruitment model. Pastors and coordinators received training by telephone and email. Promotion consisted of brief presentations to the congregation and the distribution of enrolment forms. The completed forms were sent to the AHS-2 office for processing and enrollees were mailed a questionnaire. On return of the completed questionnaire participants in non-Black churches received a personalized enrolment certificate and an AHS-2 ballpoint pen.

Based on pilot study results, the process in Black Churches was more personal. Most pastors and coordinators attended regional training sessions conducted by senior Black researchers, questionnaires were personally distributed in church, group sessions to complete the questionnaire were encouraged, and a follow-up phone call was made to non-respondents 4 weeks after they had received a questionnaire. Participants received $10 for returning a completed questionnaire. In addition, coordinators and pastors received a financial incentive of $200–$1000 pro-rated on church size and percentage of local goal achieved.

Reminder postcards were mailed to all non-responding subjects at 4, 7 and 10 weeks following the distribution of the questionnaire. In year two, the local recruitment model was supplemented with a national advertising campaign and featured articles in church magazines mailed to 300 000 Adventist households, presentations at regional church convocations and on Adventist TV stations. All advertising materials included a website and a telephone number for enrolling. Finally, a single direct mail invitation was sent to church members who did not respond to the initial church promotion.

How often will study subjects be followed-up?

The various phases and schedule of AHS-2 is found in Web Table 1. The first 5 years of the study concentrated on cohort assembly, collection of baseline lifestyle and health history data, quality control of the data and validation studies for the questionnaire. Planned follow-up of the cohort during the second and third 5-year phases, 2006–10 and 2011–15, will involve cancer incidence and mortality outcome ascertainment and periodic re-measurement of diet.

Morbidity and mortality follow-up

Follow-up of morbidity and mortality outcome is accomplished in several ways: identified by participant self-report followed by obtaining hospital records, linkage with State Tumor Registries and linkage with the National Death Index in 2007 and 2010.

Tumour registry matching

To find incident cancers in the US and Canada-wide AHS-2 population, we will computer match with every state and provincial tumour registry during 2007–10. This challenging process has never previously been attempted. Because each state registry has its own set of requirements and application process the approval process is time consuming. However, with the support of the North American Association of Central Cancer Registries (NAACCR) and building on our pilot experience with six tumour registries, we expect the process will be streamlined in the next few years, thus also benefiting other national cancer studies. A trained researcher/computer programmer travels to each state and uses identical protocols and soundex-based LINK-PLUS software (CDC) for the matching process. The possible matches are then resolved with software developed by AHS-2 and even with larger registries this process was completed in 4–5 h. A preliminary analysis suggests that we will miss only 2–3% of cases.

Hospital history form

As a back up to tumour registry matching, every 2 years we mail a four-page Hospital History Form (HHF) to participants to collect self-report information of hospitalizations and diagnoses of cancers, heart attacks, stroke and diabetes during the previous
2 years. Limited additional data on lifestyle and demographic factors is also collected. In 2004, the first HHF was mailed to the 37,000 participants who had been enrolled for at least 2 years. The second HHF mailed in 2006 included additional questions about sun exposure.

Clinics in churches
Subject to the availability of funding, during years 2008–10, we plan to conduct clinics in 2000 churches to collect fasting blood specimens and subcutaneous fat from much of the cohort. Three mobile clinic teams with two technicians each will travel from church to church testing about 35 subjects each day. The feasibility of this plan and the methods to arrange clinics, schedule subjects, obtain, ship and store biological specimens have been thoroughly and successfully tested. The bio-repository will enable us to use biological variables as prospective exposures to complement dietary analyses and provide additional information about mechanisms and to correct biases resulting from measurement errors using recently described methods.

What has been measured?

Main questionnaire
The comprehensive lifestyle and health questionnaire was developed after extensive testing and validation studies for diet and physical activity. The self-administered questionnaire is quite lengthy and takes on average 1.25–3.5 h to complete. It consists of nearly 2000 data fields divided into sections for medical, diet, physical activity, female history, supplement use and vegetarian food consumption (Web Table 2).

The food frequency component is the largest and most important part of the questionnaire. After preliminary studies and analysis, 130 food frequency items were selected to comprise the 26 nutrient/phyllochemical/mineral indices necessary to address the major hypotheses, and to include all foods and food groups commonly consumed. For each index we identified 3–4 key variables.

Questionnaires are manually edited initially to detect skipped pages, poor erasures or improperly filled in dates. For moderate amounts of missing data rescue telephone calls are made or the missing blank pages are re-mailed. We then use the NCS 500i scanner to optically scan the questionnaire data to a computer file and take an electronic image of each page for archiving. A random 10% sample of all subjects with missing data on any of 80 key variables was telephoned to fill-in missing data. This can then be used for accurate multiple imputation.

Calibration study
A calibration study of 950 participants (850 now enrolled), to conclude in 2007, provides validation data for self-reported diet, physical activity and sun exposure. A two-stage random selection process, first by church and then within church was used to select 500 white and 500 black participants. Slight over-sampling compensates for a 10% drop out after selection. This study is used to provide estimates of the validity of the food frequency data, and will assist with the correction of biases due to measurement error.

During a period of 1 year, each subject provides two sets of three 24-h dietary recalls and two 1 week physical activity recalls, 6 months apart. In the middle of the dietary recalls subjects complete another full food frequency questionnaire and attend a clinic at their church. A mobile team of two technicians process 5–10 subjects per day. An over-night urine sample is collected and aliquoted, blood pressure and body composition are measured. Blood is drawn and a subcutaneous sample of fat is taken. For the last 500 subjects, we used a Minolta Chroma-meter to measure sun exposed and unexposed skin tones. This provides an index of tanning to help validate sun exposure. Biological specimens are shipped back to Loma Linda for aliquoting in straws and are frozen in liquid nitrogen while awaiting analysis.

What is the rate of loss likely to be?
Adventists in the past have demonstrated their willingness to be engaged in prospective health studies and complete relatively lengthy questionnaires. In AHS-1 (1976–88), we were able to track 98.8% of cohort members over 12 years of follow-up. In AHS-2, we devote considerable effort to minimize attrition. A key element of cohort retention is to ensure a participant’s sense of belonging to the study through regular feedback and appreciation. This includes: an annual newsletter; quarterly email communication to participants with an email contact; articles in church magazines; presentations at annual church regional convocations and promotion of the AHS-2 website.

To maintain current addresses for the participants, national change of address services are used prior to the mailing of the annual newsletter and the biennial HHF.

For the first HHF mailed to 37,000 participants there was a 90% return rate. Black members (80% return rate) appear to be more mobile than white members and require more effort to trace changes of address and telephone numbers.

The Adventist cohort has some advantages that assist us in follow-up: we use the local church congregation unit to communicate with and keep track of members, membership lists are maintained by each local church, and when a member moves...
from one Adventist church to another, a paper trail of church transfer is usually created. Also, many Adventists locate or retire in predominantly Adventist communities.

What has AHS-2 found?
The study was started in 2002, and by early 2007 recruitment was almost complete. Web Tables 3–5 report some baseline lifestyle characteristics and prevalence data. Incidence data will soon be collected and will accrue to numbers adequate for analyses by 2010, when we expect to have 873 incident colon cancers, 1187 breast cancers and 1098 prostate cancers (246 in Black/African-American).

Web Table 3 reports demographic characteristics. Females compose 65% of the cohort, the mean age is 60.2 years; 65.3% are non-Hispanic white and 26.9% Black/African-American. Older persons are well represented with 2576 aged 85–99 years and 24,100 years or older. Almost 100% are Seventh-day Adventist of whom 63.7% were members of the Adventist church by the age of 15 years. (See Web Table 3)

Web Table 4 describes selected lifestyle and dietary characteristics. Notably, only 1.1% are current smokers and 6.6% currently drink alcohol. Mean body mass index was 27.4 for females and 26.8 for males.

Of particular interest is the wide diversity of dietary status in this population. Based on the analysis of 27 relevant food questions, 4.2% are total vegetarian, 31.6% lacto-ovo-vegetarian, 11.4% include fish with their otherwise vegetarian diet, 6.1% are semi-vegetarian (eat meat <1 time/week) and 46.8% are non-vegetarian. A wide distribution is also seen in the consumption of other foods; for instance, 25% drink soymilk several times per week and 66% eat nuts two or more times per week (Web Table 4).

Web Table 5 summarizes various health conditions prevalent at baseline; 83% report being in good or excellent health, 3% had suffered a heart attack and 14.5% reported a previous diagnosis of a cancer, of which 507 were colon or rectal, 1799 breast and 1209 prostate cancers (Web Table 5).

What are the main strengths and weaknesses?
Main strengths include: participants’ responsiveness and interest in health research; low levels of smoking and alcohol consumption that reduce the effect of confounding; support at all levels of church organization and cooperation of local churches that enhance the follow-up of participants; comprehensive food frequency data; a wide diversity of diet; the wide range of exposure to key variables—soy, vitamin D, calcium, dairy foods and linolenic acid; broad urban and rural geographic representation; large numbers of persons of African descent; the large and comprehensive calibration study to correct measurement error and validate key exposures and the planned bio-repository.

Two planned major components of the study are pioneering and unique in scope: conducting 2000 church-based clinics across North America using mobile teams of technicians to collect biological measures and the plan to computer match with 60 state and provincial tumour registries. Both components have been carefully planned and pilot tested for AHS-2, and both will establish tested methodologies that will benefit other large nationwide cohort studies.

Main weaknesses are: the length of the enrolment questionnaire—this discouraged many from participating; the low proportion of males, especially Black males; low representation of Hispanics largely because the questionnaire was not available in Spanish; a somewhat lower disease risk group, thus requiring a little more time to accumulate incident cases of cancers at some body sites.

Where can I find out more and what is the potential for collaboration?
The study is still in progress and access to the data is not yet freely available but the investigators would welcome collaboration on specific projects. Further details of the study are available from the study website www.adventisthealthstudy.org or by contacting the Adventist Health Study office at Loma Linda University.

Supplementary data
Supplementary data are available at IJE online.

Acknowledgements
We recognize the commitment of the 96,000 study participants in completing the lengthy lifestyle questionnaire and in follow-up. The cooperation and support of church officials, and the thousands of recruitment volunteers in churches throughout US and Canada were invaluable for the success of recruitment. We thank the primary investigators, research staff, consultants and the pilot study Tumor Registrars. The study is funded by a grant from the National Cancer Institute (5R01 CA094594).

Conflict of interest: None declared.

References


