

# Lessons from dietary studies in Adventists and questions for the future<sup>1-3</sup>

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**ABSTRACT** Comparisons of diets and disease rates between Adventists and non-Adventists, and prospective cohort studies among Adventists, have contributed greatly to our general understanding of nutrition and health. The most fundamental conclusion drawn from the Adventist Health Studies has been that maintaining a lean body weight throughout life is central for optimal health. Other contributions have included the value of nut consumption for prevention of coronary artery disease, and the roles of red meat and dairy products in the etiologies of cardiovascular disease and cancer. Although much progress has been made, many issues remain unresolved. In particular, rates of breast and prostate cancers remain high among Adventist populations despite an overall healthy lifestyle and long life expectancy. There is even some suggestion that risk of breast cancer may increase with duration of being a vegetarian. One topic that may be uniquely studied among an Adventist population is the effect of soy phytoestrogens in disease prevention. Although soy consumption has been hypothesized to contribute to the low rates of breast cancer in Asian populations, several intervention studies using high doses of soy estrogens have shown changes in breast nipple fluid that would predict higher rates of breast cancer. Also, high dairy product consumption has been associated with risk of prostate and ovarian cancers in some but not all studies. The unusually wide range of milk consumption in Adventists will be particularly informative with regard to these relations. Resolution of these issues is needed to provide optimal guidance regarding healthy diets, and the newly funded Adventist Health Study will contribute importantly in this effort. *Am J Clin Nutr* 2003;78(suppl):539S-43S.

**KEY WORDS** Nutrition, chemoprevention, Adventists, lifestyle factors, cancer

## INTRODUCTION

The Fourth International Congress on Vegetarian Nutrition provided a special opportunity to reflect on the contributions of studies among Seventh-day Adventists and to consider questions that remain unanswered and might be addressed by further research. A central rationale for such research is that the range of diets consumed by Adventists is distinct from those of the general populations of Western countries because the Adventist population includes a substantial percentage of vegetarians, who themselves consume a variety of diets ranging from the simple avoidance of meat to a strict vegan diet. Dietary studies in this population are important to Seventh-day Adventists themselves, as it is possible that intake of some nutrients might be suboptimal in diets that are otherwise healthy in many ways; examples may include inadequate intakes of vitamin B-12 and n-3 fatty acids. Dietary studies

in Adventists are also of great value to the general populations in the United States and elsewhere because they may provide unique information on certain aspects of diet that could be of universal value.

In the more than 300 papers in the bibliography of health-related research studies among Seventh-day Adventists (1), it is notable that the first 3 citations were coauthored by Drs Mervyn Hardinge and Fred Stare and provided descriptions of diets and biochemical findings in vegetarians and nonvegetarians (2-4). Thus, from the beginning of the Adventist Health Studies, an important interaction has existed between the Department of Nutrition at Harvard School of Public Health, at that time chaired by Dr Stare, and Loma Linda University, to which Dr Hardinge returned for a long and fruitful career.

Because the contributions from research studying Adventist populations are far too numerous to mention at this time, this paper will focus on several examples that have substantial importance and that have been addressed by nutritional epidemiology research groups at both the Harvard School of Public Health and Loma Linda. These examples illustrate the value of examining important topics in multiple large prospective studies. I will also comment on several questions of potential importance that can be addressed particularly well within the Adventist population.

## METHODOLOGIC STUDIES IN NUTRITIONAL EPIDEMIOLOGY

Early studies of Adventists documented both the distinct diets of this group (2-4) and the differences in disease rates compared with the general US population (5, 6). In general, overall mortality rates in Adventist populations were reduced, which may have been because of some aspects of diet, because of other aspects of lifestyle, and because of good access to medical care. Some cancers, such as lung cancer, were very low because of infrequent smoking by Adventists, and the rate of colon cancer was about half that of the United States in general, which might be related to diet. But despite the low consumption of meat and the generally

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healthy lifestyle, rates of breast and prostate cancer were not appreciably different from those in the US population as a whole. For all these reasons, it was important to study individual diets in greater detail as they relate to risk of disease. This created the need to devise dietary assessment methods that could be used in studies of many thousands of people. One of the early leaders in the field of nutritional epidemiology was Roland Phillips, who conducted seminal work on the design of food frequency questionnaires (7). His work documented that a limited number of foods selected by stepwise regression could account for a large portion of the between-person variability of most dietary variables. The first Adventist Health Study, which began in 1960 and continued until 1980, used a very limited dietary questionnaire consisting of 21 food items. Even this limited questionnaire has produced interesting findings on the relation of specific foods to disease risks. Through the work of Phillips and colleagues, the dietary questionnaire was expanded about 3-fold to allow the calculation of nutrient intakes, and this was used in the second Adventist Health Study, which began in 1976, among 31 208 men and women. Dr Phillips unfortunately died prematurely, but the commitment to the enhancement of dietary assessment methods has continued (8). This has resulted in the development of a more detailed dietary questionnaire that is being used in the recently launched third study of diet and disease risk among Adventists. These methodologic studies, while not making headlines, are absolutely critical to studies of diet and health, as they provide data on the validity of measurements, thus allowing an informed interpretation of study results, and contribute to improvements in the measurements themselves.

### **BODY WEIGHT AND MORTALITY**

In the early 1990s, the dominant view of desirable body weight, promoted by Andres et al (9) and reflected in the 1990 US Dietary Guidelines, was that gaining weight during midlife and achieving above-average weight were desirable. This belief seemed to be at odds with knowledge about the effects of weight on known risk factors and a lack of mechanistic evidence for benefits of overweight. We pointed out that studies of body weight and mortality had consistently failed to take into account reverse causation or control for confounding by smoking, or had inappropriately controlled for hypertension, diabetes, and other mechanistic pathways linking overweight with mortality (10). The analysis by Lindsted et al (11) of the relation between body weight and mortality in the Adventist population provided some of the best early evidence that the optimal body weight is below average over almost the whole life span. The Adventist population was particularly valuable for examining this issue because few participants smoked and the long follow-up (more than 20 y) reduced the impact of reverse causation. In a subsequent analysis in the Nurses' Health Study, by limiting the analysis to those who had never smoked, excluding participants who had recently lost weight, and deleting the first few years of follow-up to reduce the impact of undiagnosed disease, we came to similar conclusions (12).

### **NUTS, BEEF, AND RISK OF CORONARY ARTERY DISEASE**

Since the mid-1980s, as epitomized by the US Department of Agriculture Dietary Pyramid, the central nutritional message to the American public has been to minimize intake of fats and oils. Because they are high in fat, nuts were among the foods to be

avoided, and consumption fell substantially. However, the large majority of fatty acids in nuts are unsaturated and, as expected, higher consumption of nuts has improved blood lipids in numerous controlled feeding studies (13). Using data from the Adventist Health Study, Fraser et al (14) found that higher nut consumption was associated with reduced risk of coronary artery disease. This observation has been reproduced in the Nurses' Health Study by Hu et al (15) and by others (16). The inverse relation between nut consumption and coronary disease, supported by controlled feeding studies, has important implications because many individuals attempting to improve their health by following recommendations to reduce intake of dietary fat appear to have actually put themselves at higher risk of death.

In comparison to nuts, red meat has a much higher ratio of saturated to unsaturated fatty acids, and red meat also contains substantial amounts of cholesterol and heme iron, which has been hypothesized to increase the risk of coronary disease. In the Adventist Health Study, beef consumption was associated with higher risk of coronary disease, particularly among men (17). We also found red meat intake to be associated with coronary artery disease among men in the Health Professionals Follow-up Study (18).

### **DIETARY FAT AND BREAST CANCER**

A strong correlation between national per capita intake of fat and rates of breast cancer (19) led to the hypothesis that dietary fat, and possibly red meat in particular, is the primary reason for the high rates of this cancer in Western countries. Indeed, the need to test this hypothesis has been a key motivation for the development of large prospective studies of diet and disease, such as the Adventist Health Studies and our large cohorts. Thus, early publications from these studies examined dietary fat in relation to risk of breast cancer, and the findings have consistently not supported the hypothesis (20, 21). The Adventist Health Study, a central part of a collaborative project to pool the results of all large prospective studies of diet and cancer, has again confirmed the lack of association between fat intake in mid- to later life and risk of breast cancer (22). To this point in time, almost no prospective studies have evaluated dietary fat in childhood and early adult life. This is potentially important because we know from Japanese atomic bomb data that the breast tissue becomes almost refractory to the carcinogenic effects of ionizing radiation after age 40 y (23).

### **OVERALL IMPACT OF LIFESTYLE FACTORS**

Fraser and Shavlik have recently examined the potential of multiple healthy diet and lifestyle choices to increase life expectancy (24) using 34 192 California Adventists followed for mortality from 1976 to 1988. No history of smoking, avoidance of overweight, regular physical activity, nut consumption, and a vegetarian diet were each associated independently with longer median life expectancy. Interestingly, the magnitude of benefit for regular consumption of nuts, lean body mass index, and regular exercise was substantially greater than for vegetarian status itself. Among women, hormone replacement therapy after menopause was also associated with long survival. Taken in combination, these variables could account for up to a 10-y difference in life expectancy. Overall, men in this Adventist population lived  $\approx 7.3$  y longer than the average white California man, and women Adventists lived 4.4 y longer. Still, the data suggested that the Adventist population was

losing more than 4 y of life on average because of suboptimal lifestyle choices.

Using a somewhat different analytic approach, we have also been conducting a series of analyses examining the combined effects of dietary and lifestyle choices on risks of coronary artery disease, diabetes, and colon cancer (25–27). In these analyses we defined a low-risk group and then asked what percentage of disease might be avoided if the whole population were to adopt these behaviors. For coronary artery disease studies, the low-risk group was defined as nonsmoking status, body mass index below 25 kg/m<sup>2</sup>, half an hour per day of moderate to vigorous activity, good diet (low in *trans* unsaturated fatty acids and glycemic load, and high in polyunsaturated-to-saturated fat ratio, cereal fiber, and folate), and moderate alcohol consumption. We estimated that adoption of these variables could prevent 82% of coronary artery disease among women in the Nurses' Health Study population. A similar set of behaviors was associated with a more than 90% lower population rate of type 2 diabetes. With the inclusion of low red meat consumption, these variables were associated with a 71% lower population rate of colon cancer among men in the Health Professionals Follow-up Study. The fundamental conclusion is that the potential for disease reduction and improvements in longevity by diet and lifestyle changes is large. Unfortunately, this receives relatively little attention and investment compared with pharmacologic treatments of risk factors, which is enormously expensive and has much less health impact (28). The dietary advice given to the US public as the Food Guide Pyramid, which emphasizes reduction of all forms of fat and high intake of all forms of starch, represents a lost opportunity; adherence to this advice is not associated with overall reduction in risk of chronic disease (29, 30).

## QUESTIONS FOR THE FUTURE

### Soy consumption and risks of cancer

Soy and many products made from soy contain substantial amounts of several estrogenic substances, including the isoflavones genistein and daidzein. Because they can occupy estrogen receptors but have lower activity than endogenous estradiol, they can under some circumstances act as antiestrogens and have thus been hypothesized to reduce the risk of breast cancer (31). Epidemiologic studies of soy products and risk of breast cancer have been inconsistent, and the one large prospective study, conducted among atomic bomb survivors in Japan, did not support a protective effect of soy consumption against risk of breast cancer (32). However, this study was limited because diet was assessed only at baseline and follow-up continued for over 20 y. Thus, changes in diet over that time might have been substantial, leading to misclassification of soy consumption during the later follow-up, when breast cancer incidence would be higher. Although the primary hypothesis has been for protection, under some circumstances, such as after menopause, when endogenous estrogen levels are low, or with high doses, the estrogenic effects of soy might dominate and actually increase breast cancer risk. The finding by Mills et al (20) of a nearly significant increase in risk of breast cancer with longer duration of being a vegetarian adds to the need to examine this relation in detail. Two studies of soy supplementation on characteristics of breast nipple fluid have added to concerns about possible adverse effects (33, 34) of soy estrogens. During 6 mo of supplementation with soy estrogens, the volume of breast fluid and abnormal cytology of ductal cells

increased. A recent study among Japanese-Americans living in Hawaii has raised the possibility that long-term soy consumption might lead to reduced cognitive function in later life (35). Because estrogens do appear to play a role in maintaining cognition, it is not implausible that an antiestrogen substance would have an adverse effect; thus, this issue clearly deserves further evaluation.

Partly because of the low rates of prostate cancer in Asian populations and some suggestive studies in animals, soy estrogens have also been proposed to reduce the risk of prostate cancer. The relation between soymilk intake and incidence of prostate cancer was evaluated in the 1976 Adventist Health Study (36), and a marginally significant inverse association was seen. Although men who consumed soymilk more than once per day had a 70% lower risk of prostate cancer, this finding was based on only 3 cases. These tantalizing results reinforce the need for additional data based on a more complete assessment of soy product consumption.

If soy estrogens were shown to be effective in reducing risk of breast or prostate cancer, this would have important implications because soy protein can readily be incorporated in most diets. Evidence of overall benefit would also raise important questions about optimal doses and the temporal aspect of soy intake in relation to cancer incidence. The Adventist population is particularly well suited for the study of soy consumption and chronic disease incidence because of the wide range of soy intake. Within most Western populations, soy consumption has been too low to study the health consequences, although there have been some increases in consumption recently. Within Asian populations, soy consumption is likely to be part of a lifelong dietary pattern, making distinguishing between effects at different ages difficult. In contrast, soy consumption in an Adventist population is often related to religious conversion, which allows the evaluation of age-specific effects. Detailed data on soy consumption are being collected within a new Adventist cohort currently being enrolled; the data should be highly informative over the next decade. This would be a particularly good setting in which to evaluate the relation between phytoestrogens and cognitive function because the potential sources of confounding would be different from those among Japanese-American groups in Hawaii.

### Dairy consumption and risks of prostate and ovarian cancer

In many studies, intake of dairy products has been positively associated with prostate cancer incidence, although prospective studies are relatively few. Initially, the fat content of these foods was thought to be responsible, but in more detailed analyses this has not been supported (37), and calcium, from either milk or supplements, has been most strongly related to incidence, especially metastatic prostate cancer. In the 1960 Adventist Health Study (38), milk consumption was positively associated with risk of fatal prostate cancer (for 3 or more glasses per day compared with less than 1 glass per day, relative risk = 2.4, 95% confidence interval 1.3–4.3, *P* trend = 0.005), whereas in the 1960 cohort, no association was seen between consumption of whole milk and overall incidence of prostate cancer (39). The apparent discordance might be due to the use of fatal prostate cancer in the earlier study and total incidence of prostate cancer, much of which will be localized, in the latter investigation. Also, the later report (reported at a time when dietary fat was the primary hypothesized risk factor for prostate cancer) evaluated only whole milk, so the top category was 1 or more glasses per day, whereas the highest

category of total milk intake was 3 or more servings per day. Low-fat milk consumption increases blood levels of insulin-like growth factor I (40), which has been associated with risks of prostate and other cancers.

Ovarian cancer is higher in countries with higher dairy product consumption, and Cramer has hypothesized that this may be due to premature ovarian failure due to chronic galactose toxicity (41). A positive association between milk consumption and risk of ovarian cancer has been seen in some case-control studies but not in others (42). Prospective data are more limited, but evidence so far does lend support to an association (16).

Because many Adventists are lactoovo vegetarians, the range of dairy product consumption in the Adventist Health Studies has been wide and thus potentially highly informative. For example, 20% of Adventist adults reported consuming 3 or more glasses of milk per day as compared with 3% of non-Adventists of similar socioeconomic status (38). The newly launched Adventist Health Study will contribute importantly to the understanding of the health effects of high dairy consumption. Distinction among prostate cancers by their aggressiveness will be important, and evaluation of calcium from food and supplements separately will allow an assessment of whether high intake of calcium itself is a risk factor for prostate cancer. In the meantime, an updated ascertainment of fatal prostate cancers in the 1976 cohort would be of great interest. The new Adventist Health Study would also be an ideal setting in which to examine the relation of soy product consumption to cognitive function.

## CONCLUSIONS

The Adventist Health Study findings have documented that healthy diets can have a major impact on health, particularly for cardiovascular disease. Important findings include benefits of nuts and adverse effects of beef consumption in men. However, major issues remain unresolved, including the high rates of breast and prostate cancer despite diets and lifestyles believed to be healthy. The newly launched Adventist Healthy Study will provide critically important evidence regarding effects of soy products, calcium intake, and almost surely other aspects of diet yet to be appreciated. 

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