The NI-HON-SAN Study

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The NI-HON-SAN Study begun in 1965, and is a comparative study of cardiovascular disease and associated risk factors in Japanese living in Japan, Hawaii, and San Francisco. Early comparisons showed the prevalence of stroke to be the highest in Japan, intermediate in Hawaii, and the lowest in California. The trends for the prevalence of coronary heart disease in these three areas on the other hand were found to be completely opposite to those of stroke. Comparisons of risk factors demonstrated no difference in blood pressure levels, whereas the mean serum cholesterol level and body mass index were the lowest in Japan. A major difference in intake of total and saturated fats was noted between these three areas with the lowest values noted in Japan.

The NI-HON-SAN Study demonstrated that a change to a Western life-style had a favorable effect in reducing stroke but conversely resulted in increase of coronary heart disease. The message to be noted is that an excessive change to a Western life-style should be avoided in developing countries, where rapid economic growth is taking place.

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As early as 1950, studies around the world were reporting geographic differences in coronary heart disease (CHD) mortality, pathology, prevalence, and incidence ⁵. Among these reports were those of significant differences in the CHD and cerebrovascular disease rates in Japan and in the United States. Gordon reported similar overall mortality for men in Japan and in the United States, but the rates for coronary heart disease and stroke were strikingly different ⁶. Reported CHD mortality among Japanese was approximately twenty percent of that among US Caucasians. Stroke mortality, appeared to be higher among the Japanese. At about the same time Japanese living in Hawaii and California were reported to have a lower overall mortality than either U.S. Caucasians or Japanese living in Japan. The mortality from CHD and stroke was reported to be intermediate between that in Japan and that among U.S. Caucasians. The levels in Hawaii were reported to be intermediate between those found in Japan and those found in California. However, the reason for these differences were not apparent. Given the major differences between countries and regions within the United States, such differences could have been secondary to differing criteria for hospitalization, diagnosis and death certification or other factors. The frequency and characteristics of diseases often differ between ethnic groups and geographical regions. It is, however, difficult to compare results found in different populations. The instruments and methods utilized to gather such data are rarely similar. In addition data on other risk factors which might affect the comparison are either not available or are not collected in a standard manner. The populations compared may also differ in ways which are difficult to compensate for. It was known that the study of migrant populations could offer significant advantages by limiting genetic variation between study groups. Since immigrants to the U.S. underwent major changes in their diet and other lifestyle factors, if the reported differences in Japanese populations living in differing environments were real, it was felt that they might offer important clues as to the

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etiology of heart and vascular disease. Thus in order to investigate these differences the NI-HON-SAN Study begun in 1965 as a standardized international collaborative effort to examine possible differences in stroke and CHD in Japanese living in Japan, Hawaii and California. 3-4. The name of this study was derived from Nippon (Japanese in roman characters for Japan), Honolulu, and San Francisco.

METHODS

Japanese immigrants to Hawaii came in three waves between 1868 and 1924. Immigration since that time has been very limited. The principal areas from which migration occurred were portions of the islands of Honshu and Kyushu in Southwestern Japan, where Hiroshima and Nagasaki are located. Of the original 180,000 immigrants to Hawaii, approximately half of the immigrants further immigrated to California or went back to Japan. At the same time some Japanese also were migrating to the mainland U.S., especially California from a wider range of areas in Japan. 5-7

The Japanese study population was drawn from a study of atomic bomb survivors from Hiroshima and Nagasaki with various degrees of radiation exposure as well as non-exposed individuals is being conducted by the Atomic Bomb Casualty Commission (ABCC) which is now known as the Radiation Effects Research Foundation (RERF). This study is jointly sponsored by the U.S. and Japanese governments. Detailed reports of the methodology have been reported previously 8-9 This cohort has been continuously followed through biannual examinations and mortality has been determined utilizing the obligatory household registry (koseki) system that exists in Japan. The population in San Francisco consisted of respondents from Japanese men enumerated in eight San Francisco Bay area counties.

The principal objective of the NI-HON-SAN Study was to attempt to confirm the findings of differences in mortality reported in previous studies using common diagnostic and analytic methods as well as to attempt to find differences in known risk factors which might help explain any differences found. The study would take advantage of the genetic similarity and obligatory household registry (koseki) system that exists in Japan. The population in San Francisco consisted of respondents from Japanese men enumerated in eight San Francisco Bay area counties.

In general, many factors potentially related to cardiovascular disease were similar in California and Hawaii Japanese men 3-10. These two populations tended to differ from the Japanese population in Japan for many of the factors. The data showed marked differences in the intake of total and saturated fat in the three populations as well as in mean serum cholesterol levels and body mass index with Japanese in Japan having lower values. Blood pressure levels in California were highest with Hawaii being the lowest. These differences, however, largely disappeared after adjustment for body mass index which was highest in California and Hawaii and lowest in Japan. Cigarette smoking and alcohol intake were highest in Japan.

The NI-HON-SAN study confirmed that the prevalence of stroke was highest in Japan, intermediate in Hawaii and lowest in California (Figure 1). The prevalence of CHD in the three site had exactly the opposite trend, with higher rates in California, and the lowest rates in Japan 12-13. The limited incidence data available are also consistent with these relationships 14-15. Autopsy studies conducted on the cohorts in Japan and Hawaii also tend to confirm these findings 16-17.

When differences in the prevalence and incidence of CHD were compared in Caucasian men from the Framingham Heart Study, Hispanic men from the Puerto Rico Heart Study and Japanese men in Honolulu, using comparable methodology and criteria, the prevalence of CHD was found to be two times greater in Framingham than it was in Honolulu or Puerto Rico. Incidence of CHD was similarly increased 18.

RESULTS

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Only limited comparisons of the populations took place after this initial cross sectional study and follow-up. Follow-up of the San Francisco cohort was discontinued and the cohort can no longer be located. No further common examinations were conducted. However, the populations in Japan and Hawaii have continued to be followed as part of independent studies of those populations. As shown in Figure 2, a comparison of the 12 year mortality from Coronary Heart Disease between the cohorts in Japan and in Hawaii revealed an age adjusted mortality rate that was 40% higher in Hawaii than in Japan (The Hawaii/Japan rate ratio calculated by life table regression was 1.41). The difference was not statistically significant, however, probably secondary to the relatively small number of cases, especially in the Japan cohort. Only about half of this difference could be accounted for by differences in known risk factors in the two cohorts. In a multi-variate analysis age, blood pressure, serum cholesterol, serum glucose, cigarette smoking, and alcohol intake (inverse) were significant predictors of CHD mortality. The associations of risk factors with CHD tended to be stronger in Hawaii than in Japan although these differences were also not significant 18.

More recently the use of standardized instruments and methodology for collecting baseline data on a number of vari-
History of MI

Stroke Diagnosed by Physician

Figure 1. Percent of Japanese men living in Japan, Hawaii and California who gave a history of myocardial infarction or stroke diagnosed by a physician at the baseline NI-HON-SAN study examination.

Figure 2. Age adjusted 23 year CHD mortality rate per 1000 members of the original NI-HON-SAN cohorts in Hawaii and Japan.
ables as part of the NI-HON-SAN study, as well as the continued collection of mortality data in cohorts of Japanese men living in Hawaii and Japan offered the opportunity to explore the relationships of various factors to long term mortality in the two Japanese populations living different lifestyles. Thus a new collaborative initiative between U.S. and Japanese scientists (the Nippon Honolulu Mortality Among Japanese International Collaboration or NIHON MAJIC) was begun to examine these relationships, beginning with physical activity, diabetes and impaired glucose tolerance. In carrying out these analyses it was discovered that the long term mortality rates for Japanese men in the cohort in Japan continue to be substantially greater than those in Japanese men in Hawaii.

DISCUSSION

The conduct of collaborative international studies of diseases and the factors which affect them remains challenging. Profound differences exist between countries, and even between regions within countries, in access to health care, in diagnostic and treatment practices, criteria for hospitalization, coding and maintenance of vital records and access of researchers to health records. Despite these problems cross cultural studies remain important tools for understanding the etiology of disease. Many of the diseases of modern society are relatively unique to, or have differing patterns in, the Western culture. As most societies around the world move at varying speeds toward a more Western model it is important that we study the consequences of such a major societal drift. Studies of migrant populations, such as the NI-HON-SAN Study, offer some special advantages in this regard. The migrant population can usually presumed to be relatively similar to the original population in genetic make-up. Migrant populations often undergo rather dramatic changes in lifestyle, which are often easily observable and measurable.

The NI-HON-SAN Study provided some of the evidence and confirmation of the relationship of almost all of major known risk factors for coronary heart disease and stroke. In retrospect it can be seen that it would have been immeasurably more valuable to both the U.S. and Japan, as well as the rest of the world, if this important study had been continued as it was started; as a standardized collaborative comparison. Even without the funding for continued standardization of methodology valuable clues continue to emerge from this study. The two studies of cardiovascular epidemiology which it spawned, the Honolulu Heart Program and the cardiovascular components of the Adult Health Study of the RERF, have been valuable scientific resources in their own right. The data gathered by the Honolulu Heart Program on the Japanese in Hawaii offer hints to the populace of Japan of one possible future for the Japanese people. Other Asian populations which have become even more Westernized offer alternative futures, some of them less attractive. As the offspring of the Honolulu Heart Program cohort and many of the people in Japan continue to adopt more and more of the Western lifestyle and the Asian American population of the United States continues to swell, the rational for newer versions of the NI-HON-SAN Study grows.

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