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This is a cohort study of American women of Hawaiian ancestry who have one of the highest incidence rates of breast cancer in the world. It is designed to see if type of dietary fat, specific sources of dietary fat, and alcohol use enhance breast cancer risk, and to determine if micronutrients and dietary fiber reduce risk.

The study is progressing reasonably well. It has recruited 8147 Hawaiian women who returned a 26-page mail questionnaire. The surveillance of these women to identify incident cases of breast cancer is being done by the Hawaii Tumor Registry, which belongs to the National Cancer Institute's Surveillance, Epidemiology and End Results Program.

Thus far, 122 incident cases of breast cancer have been identified in this cohort. Preliminary results suggest the following: 1) early menopause may decrease breast cancer risk; 2) late childbirth may increase risk; 3) menopausal estrogens may increase risk; 4) alcohol intake may increase risk; 5) high dietary fat may increase risk; 6) high dietary fiber and beta-carotene consumers may have a decreased risk.

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FOREWORD

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A. Nomura 10/22/98

PI - Signature Date

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INTRODUCTION

A. SUBJECT

Women of Hawaiian and Caucasian ancestry in the U.S. have the highest incidence rates of breast cancer in the world. Their rates surpass that of other ethnic/geographic groups in the U.S. and elsewhere (1). It is interesting to note that Hawaiians and Maoris, who are Polynesians, have breast cancer rates that are comparable to their respective white neighbors in Hawaii and New Zealand.

Many epidemiologic studies have been done in U.S. Whites to identify the endogenous and exogenous risk factors of breast cancer (2,3). They have determined that a family history of breast cancer, an early age at menarche, a late age at first pregnancy, a history of fibrocystic breast disease, radiation exposure and a late age at menopause increase the risk for this common disease. However, it is likely that some of these factors do not account for the high risk among Hawaiian women. For example, a study has shown that their mean age at first pregnancy (22.2 years) is lower than that of Caucasian women (24.1 years) living in Hawaii (4). In addition, a recent survey by our department has found that the age at menopause was 48.7 years for Hawaiian women and 49.2 for Caucasian women. These data suggest that late age at first pregnancy and late age at menopause contribute less to the high risk of breast cancer in Hawaiian women compared with Caucasian women. This implies that other risk factors are more important among Hawaiian women.

It is strongly suspected that obesity, physical inactivity, and diet (including alcohol) contribute to the risk of breast cancer, but the results of past studies are still controversial (3,5-

13). A study of breast cancer in Hawaiian women may help to clarify some of these issues. In our survey, Hawaiian women were found to be heavier (average weight of 74.8 kg) than Caucasian women (64.6 kg) which may increase their risk for post-menopausal breast cancer. As shown in Table 1, Hawaiian women consume more calories, total fat, meat items (especially pork and beef) than Caucasian women. However, they also consume less cheese, vegetables, and fruits. The consumption of less vitamins found in vegetables and fruits may increase the breast cancer risk of Hawaiians (14,15). These and other differences in the sources of nutrition (based on the consumption of specific foods and food groups) between Hawaiian and Caucasian women add to the appeal in studying Hawaiian women as another high risk group for breast cancer. Such a study would afford us the opportunity to delineate more effectively the association of diet and breast cancer, a topic of controversy in breast cancer epidemiology. Furthermore, many case-control studies of diet and breast cancer have now been done with equivocal results. These case-control studies have the potential of recall bias which is unlikely to be a problem in prospective cohort studies.

TABLE 1

Average Daily Consumption (grams/dy) of Selected

Dietary Items and Nutrients among Hawaiian and Caucasian Women

Variable	Hawaiian	Caucasian
Calorie intake (kcal/dy)	1926	1629
Total fat	76	64
Pork	44	17
Poultry	60	48
Beef	61	36
Fish	46	27
Whole milk	64	31
Skim or low fat milk	77	95
Cheese	8	20
Vegetables	88	103
Fruits	153	179

Besides the diet, it is suspected that menopausal estrogens may also increase breast cancer risk. Several studies have shown this effect with long-term use of menopausal estrogens (16-17). However, other researchers have not been able to confirm this association (18-20). It remains to be determined if the use of menopausal estrogens contribute to the high

risk of breast cancer among Hawaiian women.

B. PURPOSE

The main goal of this study is to identify a cohort of Hawaiian women for a prospective study of the association of dietary and other environmental risk factors with breast cancer. Specifically the study is designed to investigate:

1. The influence of caloric intake, type of dietary fat (saturated, monounsaturated, polyunsaturated, specific sources of dietary fat), and alcohol use in enhancing, and of dietary fiber and micronutrients in reducing breast cancer risk.
2. The contribution of particular foods and food groups (pork, types of fruit, types of vegetables) to the risk of breast cancer.
3. The role of physical activity, including an effect independent of caloric expenditure, as a protective factor for breast cancer.
4. The association of other non-dietary exposures, such as exogenous estrogen use, with breast cancer risk.

C. SCOPE OF RESEARCH

Since 1988, a substantial amount of developmental work has already been done for this planned study, because the Hawaiian population was included in the preliminary planning for a large mult-ethnic cohort study (8 ethnic groups) in Hawaii and Los Angeles. This cohort study is now funded by the National Cancer Institute and includes African, Hispanic, Japanese and Non-Hispanic White Americans. The Chinese, Filipinos, Hawaiians and Koreans were

excluded to increase the population base for the remaining groups and to identify large numbers of cases for several cancers in each ethnic group included in the 5-year study. However, for Hawaiian women, there will be a sufficient number of cases in four years for meaningful analysis of their most common cancer site, breast cancer.

Thus one of the strengths of this study is that we have already completed most of the developmental and preparatory work. The study will closely follow the protocol developed for the multi-ethnic cohort study because the methods have been tested and because this will facilitate comparisons of Hawaiians with African, European, Hispanic and Japanese and Non-Hispanic White Americans later. The following brief chronology provides an overview of our preliminary work.

1. **Questionnaire development**. The multi-ethnic cohort questionnaire is a self administered instrument, designed to assess dietary and non-dietary factors of interest. The dietary section of the mailed questionnaire is a modification of the face-to-face dietary interview used for many years in Hawaii. To develop the self-administered questionnaire, three-day measured food records from 500 subjects (60-65 men and women, 45-75 years of age, from each of the initial 8 ethnic groups of interest) were obtained. These food records were utilized to identify those food items contributing $>85\%$ of the average intakes of nutrients of particular interest for each ethnic group and formed the basis of the dietary component of the study questionnaire. The questionnaire underwent over six revisions and was initially pre-tested in wording and format to ensure that it can be understood and completed by persons with less than a high school education. A large pretest was then conducted in 1989 in which trained interviewers sat with more than 70 subjects while the

subjects completed the questionnaire. This helped to identify any ambiguities and problems with the self-administered questionnaire. It was subsequently pilot tested in a large mailout to some 12,000 subjects in Hawaii and Los Angeles County in 1989-1990.

Based on results from 3-day measured food records, revisions and pretests, and the pilot study, we made several decisions regarding the grouping of foods, the frequency categories to be used, and the inclusion of portion sizes in the questionnaire. In order to obtain better assessments of specific carotenoids, vitamin C, and components of fat, foods were asked as a group only when they are very similar in nutrient composition. For example, carrots are asked separately; whereas yellow-orange squash and pumpkin are asked as a grouped item. To obtain more precise estimates of daily intakes, we included 8 frequency categories for foods and 9 for beverages. The frequency categories are also comparable to those used by other investigators (21). To minimize misclassification of intake, we asked subjects to select their usual portion from 3 possible sizes instead of using a standard or household portion size. Results from the pilot study showed that about 50% of subjects within each ethnic-sex group would have been misclassified on most items if we had assigned a single portion size to every food item (i.e. if a medium size was used as a standard portion).

Since the size of the cohort necessitated optical scanning of the questionnaire, it was developed with this technology in mind and with consultation from National Computer Systems (NCS), manufacturer of the scanner to be used. This approach has been used by others and found to be highly satisfactory (Willett W., personal communication).

2. **Source of Subjects for Pilot Study.** The Driver's License Files for the state of Hawaii and Los Angeles county were selected as the sampling frame for the cohort because

these files include, in each geographic area, a majority of all persons in the age range for the study, contain information on age and sex, and encompass all socioeconomic strata. Thus, these files provide the basis for a broadly-based cohort with a wide range in levels of exposure to risk factors of interest, particularly dietary. In both Hawaii and Los Angeles, we have obtained official access to these files for this research project.

Because the Driver's License files do not contain information on ethnicity, we compiled ethnic-specific surname lists by matching surnames with ethnicity from several sources, including the multiethnic cohort in Hawaii.

In addition, we have the access through the State of Hawaii to the Voters' Registration lists. This list identifies all registered voters in Hawaii who have any Hawaiian ancestry, as required by the Office of Hawaiian Affairs.

3. **Pilot Study**. In 1989-1990, we conducted a large pilot study including some 12,000 subjects in Hawaii and Los Angeles County. In this pilot, 1,000 questionnaires were sent to Hawaiians. Two additional mailings went out to nonrespondents.

The response rates to this pilot study by area for the four groups participating in the funded study and for Hawaiians are given in Table 2.

Table 2

Response Rate (%) by Ethnicity and Study Area

Ethnic Group	Hawaii	Los Angeles
African American	--	30.0
Non-Hispanic White American	70.5	49.3
Hawaiian American	47.2	--
Hispanic American	--	28.6
Japanese American	72.6	45.2
Total	63.0	38.8

For a 22-page questionnaire, with 12 pages of dietary information, mailed to a sample of the general population, this response exceeded our expectations. For example, in the Women's Health Study in Iowa (22), the response rate from a considerably more homogenous sample (mostly Non-Hispanic White) was 43%; and, in a recently established cohort in the Netherlands (23) (which followed substantial advance publicity, but only one mailing), the response rate was 35%. It should be noted that a high response rate, though desirable, is not vital to the proposed study, in that the comparisons are internal. However, as noted earlier, it is important that the cohort have a broad representation of participants for maximal range of exposures as well as greater generalizability of the findings. This appeared to be the case in the pilot study.

4. **Reproducibility of the questionnaire.** To ensure that the self-administered questionnaire adequately measures the dietary pattern of the study groups of interest, several substudies have been conducted. First, the self-administered questionnaire is modeled after a

face-to-face dietary questionnaire designed for a multi-ethnic population (24) which has been demonstrated to be reproducible and valid (25-27). Second, the reproducibility of the self-administered questionnaire has been assessed by repeat completion of the questionnaire by some 300 subjects in Los Angeles (from the four ethnic groups in the funded study) within 6 months of when they initially completed the pilot study. The correlations of most nutrients measured were between 0.5-0.7, comparable to other reproducibility studies on diet history methods (26,28,29). The correlation coefficients for most nutrients were similar for the different ethnic groups suggesting that they are unlikely to be different for Hawaiians.

D. BACKGROUND OF PREVIOUS WORK

1. **Earlier Studies**. Research on dietary and other lifestyle risk factors for cancer has been conducted by our investigators in Hawaii for more than 15 years. This research effort has included studies of cancer risks and dietary correlates among migrant populations (30-31), the relationship between dietary factors and cancer risk by specific sites in different ethnic groups (32-37), and the relationship of exogenous and endogenous hormones to cancer risk (38-39). Our data suggest a positive association between dietary fat, body size, and female breast cancer (40-42), but further work is needed to clarify these associations.

2. **Dietary Methods.** We have been active in efforts to extend and validate methods for the collection of dietary information in epidemiologic studies. We have developed a face-to-face diet history method, including both frequency and portion size information, that is applicable in multiethnic populations (24), and we have demonstrated the reproducibility and validity of this approach (25-27). Most recently, we compared estimates of nutrient intakes

from food records with those from diet histories in the same subjects, and found intraclass correlations in the general ranges of 0.4-0.8 for dietary fat and vitamins in both men and women of five ethnic groups including Hawaiians (27). This compares favorably with other standard methods (21). We have also reanalyzed these data based on calorie-adjusted nutrient intakes using the method of Willett and Stampfer (43).

BODY

A. EXPERIMENTAL METHODS AND PROCEDURES

Our goal was to recruit a cohort of Hawaiian-Americans in Hawaii, age 45 to 79 years old. Major activities included: identifying the sample, obtaining satisfactorily completed questionnaires, editing and computerizing the data, implementing long-term surveillance system and performing analyses for breast cancer.

The Voter's Registration lists were used to identify women of Hawaiian ancestry, as required by the Office of Hawaiian Affairs. This list was complemented by the Driver's License files. Because this file does not contain information on ethnicity, a list of Hawaiian surnames was compiled. In addition, a Hawaiian first name list was generated from a commercial book of Hawaiian names. These names were then matched to the names from the Driver's License file to identify suitable subjects.

1. **Study Instrument**. The mailed questionnaire to be used in the proposed cohort study is identical to the one now being used in the multiethnic cohort study. It resulted from the adaptation of the dietary questionnaire we used for many years in face-to-face interviews developed for and validated in a multiethnic population which included Hawaiians. This

questionnaire was modified for the pilot study and found suitable, for a mixed ethnic population since many ethnic foods are frequently eaten by more than one ethnic group. Changes were subsequently made in the dietary instrument with the exclusion of Chinese, Filipino and Korean groups from the funded study. However, we kept the Hawaiian foods such as poi, taro and lau lau in the questionnaire, so it is still designed to include food items contributing more than 85 per cent of the average intake of nutrients of Hawaiians.

Other questions that are included are lifetime smoking and drinking habits, medical history, occupational exposures, physical activity, family history of cancer, and for women, menstrual and reproductive history and use of hormones.

2. **Data Collection**. Based on our experience from the pilot study, we updated addresses with the National Change of Address system. This reduced the need to change addresses and reduced the number of undeliverables. Next, we sent a postcard to the subjects prior to the first mailing of the questionnaire, alerting them to the study and the questionnaire to follow. Mailing of this initial postcard is cost-effective because we can further reduce the number of undeliverable questionnaires.

The questionnaire is mailed in an envelope containing a cover letter, a #2 pencil to be used for filling out the form, and return envelope (business reply mail).

The initial mailing includes all eligible persons. The second and third mailings include only those persons who have not responded to the previous mailing. The second mailing is spaced about 2 months after the first, as this provides time for most respondents to return their questionnaires and for us to delete their names from the computer file before the next mailing. We then call the subjects who did not respond to the second mailing to boost the response rate

for the third mailing. All mailings are being done by local mailing houses, as was done in the pilot study, since this provides savings over the cost of providing additional manpower to do this work.

B. RESULTS

1. Subject recruitment. Postcards were sent to 24,468 women believed to have Hawaiian ancestry. The 1,943 women who had moved out-of-state or for whom the postcards were undeliverable, were excluded. 22,525 (92.1%) remained in the study and were sent the questionnaire. After three mailings, a total of 10,069 (44.7%) responded and returned the mailed questionnaire. Even though every effort was made to identify Hawaiian women based on Hawaiian surnames and use of the Voters' Registration list of Hawaiian women, 1546 respondents did not have Hawaiian ancestry based on their answers in the questionnaire. They were excluded from the study. The study cohort then consists of 8523 women with native Hawaiian ancestry.

2. Data entry. The questionnaires have been designed for automated data entry using high-speed optical scanners that are available at our institution. As a result, when the completed questionnaries are received from the study participants, they are scanned. Recently, we have completed the edit programs to check for internal inconsistency and to identify any discrepancies in the response recorded by study subjects. Each questionnaire is being systematically checked with the edit program by our research staff.

Thus far, 376 or 4.4% of 8,523 women had unusable questionnaires. Among the 8,147 remaining women, 357 already had a diagnosis of breast cancer, so they were also excluded.

Consequently, 7,790Hawaiian women remained in the study.

3. Surveillance. We will follow this cohort to determine cancer occurrence and mortality. We are well equipped for surveillance of cancer since the Hawaii Tumor Registry is a statewide, population-based registry and is included in the NCI's SEER Program. In addition, the Registry is part of the Cancer Research Center of Hawaii. The registry reports all new cases of cancer, and follows patients for survival information. We will follow the cohort for cancer occurrence by computer linkage to the tumor registry to identify newly-diagnosed cancer cases. To identify deaths occurring in the study areas and elsewhere in the U.S., we will use the state death files of Hawaii and the National Death Index. Thus far, we have identified 122 incident cases of breast cancer among the women who have participated in this study.

Preliminary data are available on the association of various exposures with breast cancer. All of the data in these tables have been adjusted for age. Table 1 suggests that among the 5,110 women who had undergone menopause, the risk of breast cancer was lower (0.7) for those who had menopause before the age of 45.

Table 1

Age at Menopause and Breast Cancer

Age at Menopause	No. of Cases	No. of Women	Relative Risk	95%Confidence Interval
45+ years	63	3126	1.0	--
<45 years	26	1984	0.7	0.4-1.1

Table 2 presents the association of age at first birth with breast cancer risk. Women who gave birth at age 21 or later or who did not have children, had a greater risk than women who gave birth before the age of 21.

Table 2

Age at First Birth and Breast Cancer

Age at First Birth	No. of Cases	No. of Women	Relative Risk	95% Confidence Interval
<21 years	37	3292	1.0	--
21-25 years	49	2667	1.6	1.0-2.5
Nulliparous	19	926	1.8	1.0-3.2
26+ years	17	884	1.8	1.0-3.3

The relation of menopausal estrogen use to breast cancer is shown in Table 3. Thirty-eight per cent of the women had taken menopausal estrogens and their risk of breast cancer was slightly higher than that of non-users.

Table 3

Menopausal Estrogens and Breast Cancer

Estrogen User	No. of Cases	No. of Women	Relative Risk	95% Confidence Interval
No	66	4663	1.0	--
Yes	51	2853	1.2	(0.8-1.7)

Table 4 presents the asociation of alcohol intake with breast cancer in Hawaiian women. Alcohol drinkers had a higher risk of breast cancer than non-drinkers.

Table 4

Alcohol Intake and Breast Cancer

Alcohol Intake	No. of Cases	No. of Women	Relative Risk	95% Confidence Interval
Non-Drinker	98	6313	1.0	
Drinker	22	1096	1.4	0.9-2.2

In Table 5, the women are separated into tertile groupings, based on their consumption of dietary fat, as recorded in the questionniare. Thus far, it shows that there is no clear association between the intake of dietary fat and breast cancer.

Table 5

Dietary Fat and Breast Cancer

Tertile (g/day)	No. of Cases	No. of Women	Relative Risk	95% Confidence Interval
1 <54	38	2595	1.0	--
2 54-90	42	2591	1.1	0.7-1.7
3 >90	42	2583	1.1	0.7-1.8

In Tables 6 and 7, there is a weak suggestion that a high intake of dietary beta-carotene and dietary fiber reduces the risk of breast cancer.

Table 6

Dietary Beta-Carotene and Breast Cancer

Tertile (mcg/day)	No. of Cases	No. of Women	Relative Risk	95% Confidence Interval
1 <3297	38	2595	1.0	--
2 3297-6686	43	2591	1.0	0.7-1.6
3 >6686	41	2583	0.9	0.6-1.5

Table 7

Dietary Fiber and Breast Cancer

Tertile (g/day)	No. of Cases	No. of Women	Relative Risk	95% Confidence Interval
1 <17	40	2595	1.0	--
2 17-30	41	2591	1.0	0.6-1.5
3 >30	41	2583	0.8	0.5-1.3

4. Diet Calibration Study. We are conducting a diet validation (calibration study) which will enable us to correct our dietary relative risk estimate for measurement error. We have been collecting 24-hour recalls from a sub-sample of the study subjects. Thus far, 222 Hawaiian women have completed the three 24-hour dietary recalls and the repeat dietary mail questionnaire. When this aspect of the study is completed, we will compare the self-adminsitered questionnaires with the results of three 24-hour recalls from respondents randomly selected from the cohort and representative of the study population.

C. DISCUSSION

This is an efficient study because it uses data collection instruments that have already been developed, tested and validated. In addition, the study is unique in proposing a study among one of the world's populations at highest risk for breast cancer -- native Hawaiian women.

1. Study Recruitment. The recruitment of study subjects has been completed. We were

succcessful in eliciting the cooperation of 8,523 Hawaiiian women who returned the mail questionnaire. It is estimated that by the end of the final year of the project up to 160 incident cases of breast cancer will have been identified. They should provide sufficient numbers for meaningful data analyses.

2. Surveillance. We expect a negligible rate of loss to follow-up due to out-migration. In a study in which a random sample of 2000 residents were followed in Hawaii, there was less than a 7% loss after 5 years of follow-up. For the native Hawaiian population, this number is expected to be much lower because relatively few Hawaiians migrate elsewhere. We plan to keep in touch with the participants by requesting updated addresses by means of the National Change of Address System. This would allow us to identify those respondents who move away from Hawaii. We will implement other follow-up procedures including matching those lost-to-follow-up with files from voter's registration, driver's license, credit bureau, and the Health Care Finance Administration to check for out-migration. With these programs in place, it is expected that the study will achieve its goals or purposes, as described on page 8 of this Annual Report.

D. RECOMMENDATIONS IN RELATION TO STATEMENT OF WORK

Linkage with the Hawaii Tumor Registry has been accomplished with the identification of the first 122 incident cases of breast cancer in the cohort of Hawaiian women in this study. The linkage will continue on an ongoing basis to identify additional cases for the duration of the study. Preliminary data analysis has been completed, as reported in the section on surveillance (pages 17-21). Further analysis will be done with the accumulation of additional incident cases. These activities will continue during the 5th year of this grant, as indicated under Task 4 in the

Statement of Work.

CONCLUSIONS

We have recruited 8,523 Hawaiian women into the study. Of these, 7,790 have usable questionnaires and were not prevalent cases who were already diagnosed with breast cancer. As a result, we will be able to conduct a long-term prospective study of breast cancer in this high risk population. Thus far, 122 incident cases of breast cancer have been identified.

Preliminary results, after statistical adjustment for age, show the following:

1. Early menopause may decrease breast cancer risk;
2. Late childbirth, especially after age 25, may increase risk;
3. Menopausal estrogen users may have an increased risk;
4. Alcohol drinkers may have an increased risk;
5. High dietary fat consumers may have an increased risk;
6. High beta-carotene consumers may have a decreased risk;
7. High dietary fiber consumers may have a decreased breast cancer risk.

The study is designed to continue at least one more year, during which time more incident cases should be identified to provide more meaningful data.

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